Cover Page

I N D E X

**VMAC Meeting**
**January 31, 2005**

Facilitated by Dr. Arthur Craigmill, Chair



KEYNOTE: “---” denotes inaudible in the transcript.
“*” denotes word was phonetically spelled.

P R O C E E D I N G S

(8:10 a.m.)

## Welcome/Background

**Dr. Stephen Sundlof**

DR. SUNDLOF: Good morning, everyone, and welcome to the Veterinary Medicine Advisory Committee. Today we are going to be discussing ProHeart 6 and we have a full house here, and so it is very good to see all these people here. Before we go ahead and start, Aleta Sindelar has a few housekeeping issues to go over with you. So I am going to hand over the microphone to Aleta.

MS. SINDELAR: Okay. Thank you. First, there is a conflict of interest statement for the Advisory Committee to be read which covers the -- any perceptions or documentation of possible conflicts of interest. The following announcement addresses the issue of interest with regard to this meeting and is made part of the public record to preclude even the appearance of a conflict of interest at this meeting on January 31st, 2005. Federal conflict of interest laws preclude the participation of committee members and consultants in Advisory Committee meetings if they have a conflict of interest unless a waiver from exclusion is granted by the agency. The Associate Commissioner for External Relations FDA has appointed Dr.

Charles Bennett, Dr. John Glisson, Dr. Samuel Groseclose, Dr. Michael Luster, Dr. C. Thomas Nelson, Dr. Michael Peterson, Dr. Gatz Riddell, and Dr. Lauren Trepanier as temporary voting members for this meeting.

Based on the submitted agenda for this meeting and a review of all financial interests reported by the committee participants, it has been determined that all interests in the firms regulated by the Center for Veterinary Medicine which have been reported by the participants present no potential for a conflict of interest at this meeting with the following exceptions. Dr. John Glisson discloses consulting with the sponsor; magnitude is less than 10,001. Dr. Katrina L. Mealey discloses consulting with the competing firm; magnitude is less than $10,001. She discloses a grant with a competing firm; magnitude is less than 300,000. Dr. Mealey discloses one speaking interest with a competing firm; magnitude is less than $5,001. And a speaking interest with a competing firm under negotiation; magnitude is less than $5,001. Dr. Mark G. Papich discloses two consulting interests, both with competing firms and both interest are less than 2,000 -- excuse me, $10,001 each. Dr. Papich discloses two grants. Both are with a competing firm; both are less than 100,000 each. Dr. Richard Sams discloses one consulting interest

with a sponsor under negotiation; magnitude is less than $10,001. Dr. Sams discloses one contract with the sponsor under negotiation; magnitude is less than 100,000. He will be granted a limited waiver and will not vote. In accordance with 18 USC 208(B)(3) a waiver has been granted to Dr. John Glisson, Dr. Katrina L. Mealey, and Dr. Mark G Papich. Under the terms of the waiver, Drs. Glisson, Mealey, and Papich will be permitted to participate fully in discussions and deliberations to accept the safety of the drug product voluntarily recalled and make recommendations with regard to the agency's risk management strategy. Dr. Richard A. Sams will be permitted to fully participate in discussions to address the safety of the drug product voluntarily recalled and make recommendations, but will not vote.

In the event that the discussions involve specific interests, products, or firms not on the agenda for which FDA's participants have a financial interest, the participants are aware of the need to exclude themselves from such involvement, and their exclusion will be noted for the public record. With respect to all other meeting participants, we ask in the interest of fairness that they address any current or previous financial involvement with any firm whose products they wish to comment on.

Two housekeeping notes. I would like to make sure everyone knows that the parking is free, but there is a pass code that you will need to punch in. If you are in the garage, please press the pound key and 1204. That is 1204. If you are not in the garage, please do not press the pound key. Number two, we have a very busy schedule ahead of us. We would appreciate if everyone sticks to their time limit. Thank you very much. Steve, thank you.

DR. SUNDLOF: Thank you, Aleta. Okay. We will begin with a series of presentations. Let me just go first of all and introduce the people who are sitting at the front. I am Steve Sundlof. Sitting right to my left is Jenny Gresock. She is with the Office of Chief Counsel of the Food and Drug Administration. Margarita Brown is the veterinary medical officer who reviews the adverse drug event reports that we are going to be talking about extensively today, and Dr. Lynn Post who is the Director of the Center -- I'm sorry, the Office of -- the Division of Surveillance. It is tough living in a bureaucracy.

(Laughter.)

DR. SUNDLOF: And the Office of Surveillance is the office that conducts post-market approval studies like the ones we are going to be talking about today. So those are the folks in the front panel here.

(Slide.)

The purpose of today's meeting is to review the safety of ProHeart 6, which is a heartworm preventive drug approved for use in dogs. The sponsor, Fort Dodge, has voluntarily recalled ProHeart 6 from the market at the urging of the Center for Veterinary Medicine because of reports from veterinarians, pet owners and others filed through the Center's adverse drug experience reporting system. They raised questions about the product safety. So in a few minutes you will be hearing a description of the ADE system, and so let me just define ADE right now. That is adverse drug event or adverse drug experience. We are going to primarily refer to them as adverse drug events today. So ADE is adverse drug events, and we will be discussing those extensive as they pertain to ProHeart 6 today and to some other similar heartworm preventive products.

(Slide.)

I want to introduce the members of the panel here today, the Advisory Committee meeting, and so let me go through the list and tell you a little bit about these folks. Our chairman is Dr. Arthur Craigmill. He is an expert in veterinary toxicology and represents that discipline on the VMAC in addition to his role as chairman,

and we welcome you, Art, as the new chair. Also today with us is Susanne Aref, but I don't see her here, so maybe she didn't make it. Susanne Aref is our expert in biostatistics at Virginia Polytechnic Institute and State University. Dr. Corrie Brown is with us today. She is an expert in pathology with the University of Georgia. She made it up from the south, but apparently Skip Jack didn't. So Sherman Skip Jack, he is our expert in minor use in minor species. Maybe he will be able to get here later today. I don't know. Representing the consumers is Greg Jaffe, and Greg is with the Center for Science and Public Interest. Dr. John McGlone, there's John, is an animal science expert and does represent animal science as a discipline on the VMAC. Dr. Katrina Mealey is an expert in companion animal medicine and represents that discipline. She is from Washington State University. Lisa Nolan is an expert in veterinary microbiology with Iowa State University. Mark Papich is an expert in pharmacology with North Carolina State University, and Dr. Richard Sams is an expert in chemistry with the Ohio State University.

In addition to the regular members we also have some consultants with us today because of the nature of the subject. Really we are going to be going through a number of various disciplines. So we have with us today

Charles Bennett who is an expert in pharmaco-epidemiology with the Feinberg School of Medicine and with the Midwest Center for Health Service Policy Research. Dr. John Glisson is an expert in Avian Medicine with the University of Georgia, and I think like Dr. Jack was unable to get out of the Atlanta. Dr. Tom Nelson is a heartworm expert and President of the American Heartworm Association -- or, I'm sorry, American Heartworm Society and with the Animal Medical Center in Anniston, Alabama. Dr. Michael Peterson is an expert in zoonotic and infectious disease epidemiology with the Office of the Assistant Secretary of Defense. Dr. Gatz Riddell is an expert in food animals, food animal medicine, with Auburn University, and Dr. Lauren Trepanier is an expert in dramatic differences in drug metabolism with the University of Wisconsin. So that concludes the list of experts who will be helping us with this, with the decisions that we will be making today. Oops. Should have done that sooner.

(Slide.)

Just to talk a little bit about CVM's mission, and this is taken directly from our mission statement. It is part of our mission statement. Not the whole thing, but it says "We foster public and animal health by approving safe and effective products for animals and by

enforcing other applicable provisions of the Federal Food, Drug, and Cosmetic Act and other authorities." So a lot of the things that we will be talking about today tie directly back to this mission. Not only our mission to protect animal health, but also how we enforce those responsibilities through the various legal channels.

(Slide.)

Our responsibility to determine a drug safety does not end after the drug is approved. We have an extensive pre-market review process that is intended to try and pick up any abnormalities or adverse events prior to the approval, and we deal with those in the pre-approval stage. But we can't always pick up all of them, as folks are well aware, and as a result there are some -- there are adverse events that occur after the approval that were not anticipated during the pre-approval stage. So we have an extensive post-approval surveillance system to try and pick up these unintended events. In this case we received several adverse events regarding this particular product, ProHeart 6, and so we will be discussing our reasons for taking the positions that we have during the rest of the day.

(Slide.)

Okay. The information we collect through our

adverse drug event system is carefully and thoroughly analyzed. We use an established review process for ADEs that provides standards and gives an ordered and structured system that can be used to analyze information and make unbiased decisions about product safety. The system CVM uses to analyze these adverse drug events is much the same as that that is used in our human counterpart, the Center for Drug Evaluation and Research; and in just a little while we will provide you with a description of how that system works, how the causality grading system is set up, et cetera.

(Slide.)

Due to our concerns from the ADE reviews, we approached Fort Dodge Animal Health and at first asked for label changes, which Fort Dodge changed. So there were label changes. Generally we asked the company to change the label if there are adverse events that were not originally listed but that appeared on post-market evaluation. Oftentimes that yields a reduction in the number of adverse drug events and has a substantive effect in improving the safety. In this case, however, even after the label changes went into effect we did not see a subsequent reduction in the number of adverse drug events. So after studying this very thoroughly the Center took the position that in light

of the fact that the adverse events were not decreasing we asked the company to voluntarily recall the product, which they did.

(Slide.)

So the reasons for this VMAC meeting is in the spirit of openness and transparency. We want to present our case in a public forum, which is this Veterinary Medicine Advisory Committee meeting. This is an important product obviously to veterinarians and to the company. We think that it deserves a very thorough discussion, and we want to be sure that all the information gets thoroughly reviewed not only by CVM, but by independent specialists on the Veterinary Medicine Advisory Committee so we can get their opinions and benefit from their experience. This is a fairly common use of an advisory committee, and this is one of the reasons that we have these advisory committees, to bring in as much outside expert opinion into the decisions that CVM makes as possible.

(Slide.)

So in conclusion, CVM has the ultimate responsibility for determining the safety of animal drugs. The amount of information that we can get about products through adverse event reports is often broad and can be complex and affected by confounding factors. We appreciate

the advice and insight of the members of the VMAC and we hope you will help us to be sure that we are making the right decisions. With that, I will close my remarks and turn the podium over to Jenny Gresock.

## Legal Framework

**Jennifer Gresock, Esquire**

MS. GRESOCK: Thank you, Dr. Sundlof. My goal today is to provide a brief look at the legal background against which CVM operates.

(Slide.)

The Center for Veterinary Medicine has the regulatory responsibility for insuring the safety of marketed animal drug products through an approval process. Drug approval depends on a showing of effectiveness, but also of safety, and today our focus is on safety. Section 512 of the Act details the requirements for new animal drug approval.

(Slide.)

When submitting an application for a new animal drug product the applicant must show that the product is both safe and effective for its intended use. For drugs used in food animals an evaluation of a drug's safety includes focusing for instance on human food safety. For companion animals target animal safety is the primary

concern.

(Slide.)

Under the Act, an applicant must submit as part of the new animal drug application full reports of investigations which have been made to show whether or not a drug is safe and effective for use. With regard to safety, an application may be refused if it doesn't contain these full reports and adequate tests by all methods reasonably applicable to show whether the drug can be safely used as suggested in the labeling proposed by the applicant.

(Slide.)

Note that the attention to labeling is a key part of the process of approving new animal drugs. The labeling for an approved animal drug product should indicate how to use the product in a safe and effective manner. The safe use of a drug may for instance require caution statements that alert the users of the product to particular species in which the drug should not be used, or the labeling may note particular effects that a veterinarian or pet owner should be aware of when using the product. In short, the labeling of an approved animal drug product must provide adequate directions for use or it is misbranded under the Act, and that means that FDA can take legal action against it. The labeling is extremely important.

(Slide.)

After a drug has been approved, CVM monitors the safety and effectiveness of the drug as it is used more widely. The law requires drug sponsors to establish and maintain records and to make reports to FDA of data relating to experience or other date and information received or otherwise obtained by the sponsor. Specifically the regulations require drug sponsors to report adverse drug experiences.

(Slide.)

What is an adverse drug experience? Note that it is any adverse event, whether or not considered drug related and regardless of whether or not the drug was used in a manner consistent with its labeling. This includes both ineffectiveness reports as well as events related to safety of the product. The regulations have special reporting requirements for adverse drug experiences that are both serious and unexpected.

(Slide.)

What is a serious adverse drug experience then? This slide highlights the types of experience that are categorized as serious. Note that they include those that are fatal or life threatening, but also those that require professional intervention.

(Slide.)

What then is an unexpected adverse drug experience? The key here is that an unexpected adverse drug experience is not listed on the current labeling for the drug or an unexpected adverse event may be much more severe or specific than a related event that is listed on the labeling.

(Slide.)

I have highlighted serious unexpected adverse events because those are the ones that must be reported by sponsors within 15 working days of receiving a report from a consumer or veterinarian.

(Slide.)

Other adverse drug experiences, those that do not qualify as serious and unexpected, must be reported in periodic drug experience reports. These are submitted every six months for the first two years after approval and then yearly thereafter. Note that consumers have no legal obligation to report adverse drug experiences. Only the drug sponsor has such an obligation.

(Slide.)

What happens when a drug product raises safety concerns? FDA has a number of different things that it can do. In some cases, FDA can request a recall under

the regulations. Alternatively, the firm may initiate a recall also under the regulations. Short of that, FDA would first try to do smaller steps. For instance, working with the sponsor on labeling and/or manufacturing changes. Fort Dodge for instance has worked closely with CVM on several labeling changes intended to make the drug safe for use. If none of these things work, FDA may issue an order withdrawing the approval of the product. Such an order would be issued based on certain findings by the Secretary. Such a finding may be that experience or scientific data show that the drug is unsafe for use under the conditions of use upon which the application was approved. That would be one of the possible grounds. Or such a finding might be that new evidence not contained in the application or not available to the Secretary until after the application was approved evaluated together with evidence available when it was approved show the drug is not shown to be safe for use under the conditions for which it was approved. These findings would follow notice to the sponsor and an opportunity for a hearing. This is the legal framework within which CVM operates.

## FDA/CVM Adverse Event Reporting

**Dr. Margarita Brown**

DR. BROWN: Good morning, everybody. I am

pleased to have the opportunity to share with you our adverse drug event procedure here at FDA Center for Veterinary Medicine. I'm one of the four veterinarians initially recruited by CVM for the sole purpose of reviewing these adverse drug events and entering them into our database. We now have seven veterinarians working at this job part time. The rest of the week six of these seven practice veterinary medicine here in Maryland and in Virginia.

(Slide.)

As you can see, we all have strong clinical backgrounds, which is really critical in understanding and evaluating these reports. Every one of us knows what it is like to be the person responsible for prescribing and administering any of these medications, and we also know the many differentials that must be considered when things start to go wrong.

(Slide.)

Our job is to review and evaluate the drug events that are sent to our office from the drug sponsors as well as from veterinarians and pet owners. We do this because there are inherent limitations in the pre-approval process, and those can't guarantee then the absolute safety and effectiveness of the approved veterinary drugs.

(Slide.)

Now recognizing that we represent the clinical approaches of at least five different veterinary schools, it is very important that we have a way of making our review process objective. We use the Modified Kramer System. It's a good tool for promoting the consistent application of the same set of standards, regardless of personal opinion. We don't just grab a causality association out of the air. We have to get there the same way each time. There are six axes or criteria that are used. The first is previous experience. What is already known about this drug and its possible reactions? The second is an alternative etiologic candidate. That is, is there something else that could be contributing or causing this event? The third is timing. Is this a consistent timing to happen with this type of reaction in this type of patient? The fourth is, is there evidence of an overdose? The fifth is dechallenge, which is what happens when the drug is removed from the system; and the sixth is rechallenge, what happens when the drug is reintroduced.

(Slide.)

When we apply the algorithm to these events in the adverse reports we add up the scores to arrive at a causality assessment score. Here are the interpretations of

the ranges. Remotely drug related are those with the negative numbers, -1 to -6. Those that are possibly drug related are 0 to +2. Probably drug related are +3 to +5, and definitely drug related +6 to +7. For those of you who are familiar with our website where we post monthly the results of the causality assessment scores for our different drug events, you will know that the only scores and the only signs that show up on that website are those that are in the positive range. That is zero and higher. None of those with negative numbers are included in that analysis.

(Slide.)

Now when we get an adverse drug event we start by pulling up the label for that drug. We look at the species and the dose labeled for its use. We look at the labeled adverse events that are known to occur. We look at our database to see if similar reactions have been reported. We look at safety studies in the Freedom of Information Summary to see what kind of leeway has be documented before adverse events are precipitated at higher doses. We look at the pharmacodynamics to understand how the drug is processed in the body and when adverse events might be expected to occur. We can also refer to published articles in textbooks and journals. What we don’t do is just think, "Well, you know, it seems like that could happen," and go on the

strength of our personal instincts. We have to use factual information.

Now if this is a newly-marketed drug we might not have a lot of information to work with as far as previous reactions are concerned. In that kind of instance we put our heads together, we discuss the information we do have, and we do our best to standardize the issues such as timing for labeled reactions. For reactions that are not labeled, the best we can do is to see if they show up at a time when the drug is at peak levels in the body.

(Slide.)

Okay. Let’s take a look at a sample adverse drug event and apply the Modified Kramer Algorithm to it. So consider that we have a four-year-old mixed breed neutered dog. He comes into his veterinarian for his wellness care. He is good health on physical exam. He has a negative heartworm test. He is given his ProHeart 6 injection at the labeled dose, seems to be fine, but four days later he starts vomiting. So first I need to find out if the adverse event, vomiting, could be an expected reaction.

(Slide.)

So let’s look at ProHeart 6's label. The labeled adverse events when it was first approved were

vomiting, diarrhea, listlessness, weight loss, seizures, injection site reaction such as itching or swelling, and fever. Okay. This complaint is for vomiting, and it is on the label.

(Slide.)

So I can clearly give this a plus one in the first axis of the algorithm, that for previous experience. It is generally recognized to occur in this species at this dose. It's on the label.

(Slide.)

Well, how about the second axis for alternative etiologic candidate? Is there absolutely nothing else that could cause this reaction? Might we expect this sort of reaction to occur spontaneously in this type of patient? Are any other drugs being given concurrently that can cause the same reaction? Is there a preexisting condition? You will notice that we need very firm evidence here to say that there is really no other candidate other than the administration of the drug. Often the strongest score we can give here is a zero. It might occur spontaneously or there might be an alternative candidate, but not a good one.

(Slide.)

We give it enough data to rule out the

possibility of a contributing factor. For example with vomiting. Well, have there been changes in the diet? Has this animal been thoroughly checked for parasites? Is there a history of vomiting in the past? Have blood values been checked and found normal?

(Slide.)

Now sometimes there has been a good physical exam, and excellent medical history and work-up are provided. In serious instances if we don't have that information we might call the sponsor or the reporting veterinarian for follow-up information. If we get that kind of complete information we might be able to score a +2 on that second axis. There is no good reason other than administration of the drug for the reaction to have occurred.

(Slide.)

But here in the real world I would like to represent a typical report and say we have no known dietary changes. We have one negative stool sample for parasites. There is no blood work. We can't really say for sure that something else is going on or isn't going on. We have to put a zero at that second position.

(Slide.)

The third component of the algorithm is

timing. Now we know from the pre-approval studies that PH 6 blood levels peak at seven to 14 days after injection. So the complaint is one of vomiting that started eight days after injection. I'm clearly able to give this a +1 at the third line for timing. It is consistent and expected.

(Slide.)

Now let's look at overdose. The way this is worded if I want to put a +1 in the position for overdose I need to know that this reaction is expected to occur in the species at this elevated dose. We will say we have safety studies showing that the drug was safely administered at three times and five times the regular dose. If there was a slightly highly dose given, but it is within that three-times to five-times range, then we cannot score anything stronger than a zero at this point in the algorithm. We are required to say that technically it was an overdose because it was higher than the approved label dose, but we do not score it as an overdose.

And let me add that we don't often score overdose for ProHeart 6 because it is given by medical professionals, either veterinarians or veterinary health technicians. It is not like you have the situation where the husband comes home early, he gives the dog its pill, then he rushes off to take the kids to their soccer game and

say an hour later the wife gets home. Oh, she dutifully remembers to give their dog their heartworm pill, and the dog has wound up with a double dose right in that instant. Or sometimes some of these medications are so delicious that the dogs will go ahead and gobble up a whole bottle full of them all by themselves. We don't usually see that happen with an injectable.

(Slide.)

Dechallenges is part of the algorithm, another one that doesn't really apply to ProHeart 6 because it refers to what happens when the drug is stopped, when it is removed from the system, or when its levels are reduced by decreasing the dose. With a six-month injectable, the drug stays in the animal's body for all that time. So it's difficult to say that when the vomiting stops in three weeks it is because the drug is no longer there. It is not like stopping a pill and seeing the vomiting stop in a few days. We can really only give this a zero in the dechallenge axis. Dechallenge is difficult, inappropriate, or impossible to assess.

(Slide.)

Rechallenge refers to what happens when the drug

is given again. This again usually gets a zero in the

ProHeart 6 reports. Well, there could be some instances where neither the owner nor the veterinarian suspects that the vomiting was caused by the injection until the same thing happens when the drug is given six months later. But unless that kind of follow-up information is given, the score here usually remains a zero for no rechallenge attempted. Again, compare this to seeing the vomiting occur several hours after every time a pill is given.

(Slide.)

So when we add up the scores assigned for this report of vomiting, which is on the label and happens during the time of peak concentration in the body, the strongest score we can give adds up to a +2, possibly drug related. I think you can see that usually this scoring system gives the benefit of the doubt to the drug. Now let's take a look at what happens with an event that is not on the label but starts showing up in the post-approval marketing, a complaint like anaphylaxis.

(Slide.)

Characterized by such things as sudden profuse vomiting and diarrhea, swollen head or face, hives, pale mucus membranes, or collapse.

(Slide.)

In many complaints as in this example,

ProHeart 6 was given along with routine vaccinations. So here you have a three-year-old small-breed dog. Again she comes in for her wellness visit to her veterinarian and is in good health on her physical exam. She has a negative heartworm test. She gets her ProHeart 6 injection at the label dose along with her annual distemper vaccination, and two hours later she breaks out in hives, her face swells up, and she collapses.

(Slide.)

Now because this reaction was not on the original label or in the Freedom of Information studies, we could only give it a zero in that first position for previous experience. How about an alternative candidate? Vaccinations are certainly known causes of anaphylactoid reactions. So we have to give a -1 score at that second axis to accommodate for the vaccination. In the third axis, timing, this was very closely associated with the injections and well within the time frame for this type of reaction. So a +1 can be assigned there. The regular dose was given, so this dose stays zero at overdose. Dechallenge and rechallenge not applicable in these reports, zero for each of those. So adding up the overall score we get a zero. That is possibly drug related.

(Slide.)

Now in some reports vaccines were not given at the same time, and neither was anything else such as a penicillin injection or a cortisone injection. We would put a zero then at that second position for alternative etiologic candidate, bringing up the total score to a +1, still possibly drug related. Such a large number of these types of reactions were reported that the label was changed in June of 2002 to include anaphylactoid reactions as adverse events. So we can now put a +1 at that first position for previous experience. Some of these dogs were closely observed after their injections, and we were thus able to put a +2 in that second position for no alternative etiologic candidate if the dog were kept inside and observed after the injection and insect exposure was unlikely. We did not have a circumstances where a dog had an anaphylactoid reaction and then was given a second dose of ProHeart 6. Again, overdose, dechallenge and rechallenge remain at zero. So a +4, probably drug related, is the highest score that could be assigned to many of these ProHeart 6 reports, and that demanded very complete reporting. No other medications administered, a patient closely monitored after administration to reach that score.

Now of course in many other circumstances you don’t have a dog that is closely monitored after these

injections. Many people, they would just take their dog home and let him outside in the yard, and in that kind of circumstance in that second axis for alternative candidate we have to leave it at a zero. So for those again the highest score we could reach would be a +2, possibly drug related.

(Slide.)

So this level of information could rarely be provided for other complaints of illness, even if labeled and expected, such as the example of the vomiting dog I gave previously, and in addition we must keep in mind that these three components of the Modified Kramer Algorithm do not really apply to ProHeart 6. That is overdose since it is given by a health professional, dechallenge because the drug remains in the body, rechallenge because the drug is rarely given again if a reaction was recognized after the first administration. So most of these complaints can only be scored as possibly drug related, even if they are expected events that begin while ProHeart 6 is exerting its peak effect in the body. I hope this review of our scoring system will serve as a basis for understanding the rest of today's presentations. Thank you.

MS. SINDELAR: We are going to proceed with the agenda since we are moving along so well with Dr. Post.

## ProHeart 6 ADEs/CVM

**Dr. Lynn Post**

DR. POST: Good morning. I am going to give an overview of the ProHeart 6 adverse drug events.

(Slide.)

The evaluation of adverse drug events falls under observational studies. In general, the advantages of observational studies are a larger and more diverse population and under actual conditions of use. The population at risk has differences in diet, genetics, breed, age, environment, and so on. In a diverse population there are many confounding factors, such as preexisting disease and concomitant medications. It is the variation in the population that makes it difficult to define a control group.

(Slide.)

Reporting rate is defined as the number of adverse drug events, the numerator, divided by the number of exposed patients, the denominator, over time. The ADE reporting rate is not an incidence rate for two reasons. First, ADEs are under-reported by the clinician because of such things as the adverse drug event may not be connected to the drug, there may be fear of litigation, just more

paperwork, and the clinician wishes to protect the client's privacy.

(Slide.)

Second, accurate data on the number of exposed patients, the denominator, is often lacking. It is only a guestimate.

(Slide.)

A reporting rate compared to the background incidents may provide a signal that there is a problem with a product. This is expected. But what happens if the reporting rate falls below background? Well, this does not prove that there is not an increased risk of the adverse drug event. The signal could still be valid. Furthermore, spontaneous ADE reports give uncertain numerators due to under-reporting with no denominator at all. The use of denominators only serves to compound the uncertainty of the numerator. Therefore, CVM has not used denominators in this presentation.

(Slide.)

Okay. Now I will go over a little of the pre-approval history. ProHeart 6 was approved in June of 2001. The laboratory studies revealed no serious adverse drug events in healthy dogs, but this does not prove that or mean that there will no adverse drug events in the post-

approval period. It only means that no adverse drug events were found in the pre-approval studies. Clinical field studies revealed several adverse drug reactions of vomiting, diarrhea, listlessness, weight loss, injection site pruritus, itching, and increased body temperature. In clinical field studies ProHeart 6 was used safely in conjunction with a variety of veterinary products, including vaccines.

(Slide.)

In the clinical field trials there were three deaths which resulted in the following precaution statement on the label: Use with caution in sick, debilitated, or underweight animals.

(Slide.)

The ProHeart 6 active ingredient, moxidectin, is also a macrocyclic lactone. Neurotoxic science for macrocyclic lactones may include seizures or convulsions. Seizures have been added to the post-approval safety information on several labels.

(Slide.)

There have been three label changes since product launch in June, 2002. Anaphylaxis/anaphylactoid reactions, depression, lethargy, urticaria -- that’s hives -- and head and facial edema were added to the label. In

November of 2002, cardiopulmonary signs associated with the administration of the product in heartworm-positive dogs. ProHeart 6 was originally approved as safe in heartworm-positive dogs.

(Slide.)

The third label change was in July of 2003, and a client information sheet and the phrase "and rare reports of death" was added to the label. Two "Dear Doctor" letters were sent out by the sponsor describing the three label changes, on in June, 2002, and the other in June, 2003.

(Slide.)

The annual number of initial ProHeart 6 adverse study reports has not appreciably decreased. I am talking about the column under initial reports.

(Slide.)

The annual reports are further broken down by initial, follow-up, and total ADE reports. That initial is in red, follow-up is in black, and total is in green, and the X axis is calendar year and quarter. The reporting pattern shows a peak frequency in each of the second quarters corresponding with heartworm prevention season. Notice that the frequency has not appreciably decreased since product launch to September 1st, 2004. The

manufacturing changes indicated by an arrow in the third quarter of 2002, and the residual solvents were removed from the formulation. The minimal residual solvent lots were in use by the first quarter of 2004, the arrow marked MRS lots. Despite the manufacturing change, again there has been no appreciable decrease in frequency as of September 1st, 2004.

(Slide.)

Of the nearly 22,000 assessments for all the clinical manifestations, more than 19,000 of them, of the clinical manifestations, have a positive causality of possible, probably, and definite. Then 32 reports were categorized as definitely drug related, and all had causality assessment scores of +6 for heartworm ineffect. The top row marked definitely drug related.

(Slide.)

Time of onset refers to the duration between administration of ProHeart 6 and observation of clinical manifestation. All clinical manifestations had a positive causality assessment represented in this slide. Approximately one-half of the clinical manifestations were with concomitants. That is vaccines and drugs. Approximately one-third of the clinical manifestations were without concomitants, and approximately one-sixth were of unknown concomitant status. The majority of the clinical

manifestations, over 15,000 of them, occur in zero to 14 days.

(Slide.)

Time of onset coincides with peak serum concentrations of moxidectin from seven to 14 days.

(Slide.)

Clinical manifestations zero to 14 days.

(Slide.)

Peak serum concentrations of moxidectin seven to 14 days.

(Slide.)

Numbers of dogs with reported ADEs. The website numbers will be larger because of extra-label use. The ADEs on the website are listed by species and active ingredient, so a product labeled for a horse could end up under a dog. As you can see, we get a lot of adverse drug event reports for heartworm preventatives, including reports of ineffectiveness. Ineffectiveness seems to involve the entire class of macrocyclic lactones, and we addressed this concern of ineffectiveness at the American Heartworm Society Meeting in July of 2004. All of the products have ineffects for heartworms, but depending on the label indications one or more of the heartworm preventatives have ineffects for hookworms, roundworms, whipworms, fleas, ticks, and mites.

Selamectin since it is applied topically also includes a lot of application site reactions, things like local hair loss. CVM worked with the sponsor to conduct post-approval studies and implement an educational program for selamectin ADEs. That would include ineffects. As a result, ADEs decreased in frequency and severity.

(Slide.)

But when we addressed the frequency of series adverse drug events such as death, you can see that there are more assessments of death associated with ProHeart 6 compared to all the monthly heartworm preventatives combined. Dr. Brown will now outline some of these serious events in more detail. Thank you very much.

**ProHeart 6 ADEs/CVM**

**Dr. Margarita Brown**

DR. BROWN: So Dr. Post has just given you an overview of ProHeart 6. Let me now take you through some of our specific concerns. Let me move this back up until we get there. You remember that this is a spontaneous reporting system, meaning that someone has to take the time and effort to fill out a report. Large numbers of reports in relatively young, healthy dogs can be what we call a signal that something is going on. Now if we are talking about reports of side effects that are simply upsetting or

inconvenient we might not be so concerned. I am not going to waste your time with those. Instead let's take a look at some of the serious reports that have been submitted for the marketed heartworm preventatives other than the complaint of ineffectiveness. Now for all the tables that follow I am including only data for events with the highest-ranking morbidity and mortality with a causality assessment score of zero or higher. That is possibly, probably, or definitely drug related.

(Slide.)

Now I know you were all paying close attention during my earlier description of the Modified Kramer Algorithm, but just as a quick reminder, we use these six axes to arrive at the causality assessment score for each clinical manifestation in the adverse drug event reports that we receive. There are seven different reviewers, and we apply the same criteria to all the adverse drug report events sent to us.

(Slide.)

We use these interpretations for each score that is reached, and I am presenting only information that falls in the category of possibly, probably, or definitely drug related, and that is a score of zero or above. I think every pet owner's worst fear is death, so let's look at that

first.

(Slide.)

This table shows you that between the approval of ProHeart 6 in June, 2001, and its voluntary recall in September of 2004, there were more than twice as many deaths reported among dogs that received ProHeart 6 -- that is 485

-- than for all the other heartworm preventatives combined -- that is 219 -- even though ProHeart 6 sales represent approximately 24 percent of the market.

(Slide.)

One of our foremost concerns has been the number of anaphylactoid reactions associated with the use of ProHeart6, and as you know those refer to sudden shock events, swelling of the head and face, sudden profuse vomiting and diarrhea, even death. As you can see, there are almost 20 times the number of such events associated with ProHeart 6, 1,820, than for all the other heartworm preventatives combined, 97.

(Slide.)

These events are occurring very shortly after administration of ProHeart 6. This shows the distribution of the onset times for these anaphylactoid reactions. You can see that almost all of them, 80 percent of them, occur

within the first three hours. Remember these are dogs that came into their veterinarian for preventative care. Most of them were examined by their veterinarian and judged to be in good health, good physical condition, before ProHeart 6 was given.

(Slide.)

For these 1,820 episodes of anaphylactoid reactions, there reporting veterinarians indicated that at the time of ProHeart 6 administration the health status was good in 1,741 of them, fair in 69, poor in three, and unknown in seven; 54 of these dogs died.

(Slide.)

Some of these dogs had at least one vaccination given at the same time as ProHeart 6 injection since they were at the veterinarian for preventive care, or they might have been given some other drug such as cortisone or antibiotic. The label clearly states in well-controlled clinical studies ProHeart 6 was safely used in conjunction with a variety of veterinary products, including vaccines, anthelmintics, anti-parasitics, antibiotics, analgesics, steroids, non-steroidal anti-inflammatory drugs or NSAIDS, anesthetics, and flea control products. In 1,816 anaphylactoid episodes, dogs did not have any concomitant drug or vaccine given. In 731 episodes they did have a

concomitant drug or vaccine, and the concomitant status is unknown for the dogs in those 273 episodes.

(Slide.)

Another category with a lot of reported reactions concerns convulsions or seizures. These may be fairly minor or occur only once, or they may be so severe and protracted that the dog requires ongoing medication or even dies. Convulsions are a known possible side effect with the class of drugs it is used for, all the monthly heartworm preventatives and ProHeart 6, and convulsions or seizures are on the label for each of them. As you can see, each of the marketed heartworm preventatives except for the ProHeart or moxidectin tablets, which are not extensively used here in the United States, has more than 100 assessments for convulsions since the time of the approval until September of 2004. But ProHeart 6 accounts for more than half or 378 of the 630 for all the rest of them combined.

(Slide.)

Approximately half of these convulsions occurred within three days after the administration of ProHeart 6. As you can see, the distribution of the onset times falls well within the time of rising or peak levels of ProHeart 6 in the body. That is seven to 14 days.

(Slide.)

For these 378 episodes of the convulsions, the reporting veterinarians indicated that at the time of ProHeart 6 administration the health status of the dogs was good in 302 of them, fair in 64, poor in seven, and unknown in the remaining five; 61 of these dogs died.

(Slide.)

In 87 episodes, dogs did not have concomitant drugs or vaccines, and in 215 episodes they did. The concomitant status for dogs in the 76 episodes is not known.

(Slide.)

Let’s look at liver problems next. There are many ways that liver problems can be manifested or diagnosed, so I have chosen to use the most specific markers in our database; elevations in an enzyme found in the blood called SGPT/ALT, and lesions found by pathologists on examination of biopsies of the liver or in the livers from dogs that died. Here again you see that the number of SGPT/ALT elevations and liver lesions reported for ProHeart 6 since in the first three years of its approval, at 192 and 65, surpass those reported for all the other marketed heartworm preventatives combined since 1987. That is 145 and 30.

(Slide.)

For the 192 SGPT/ALT elevations the reporting veterinarians indicated that at the time of Proheart 6 administration the health status of the dogs was good in 149 of them, fair in 36, poor in six, and unknown in one; 38 of these dogs died. Among the 65 dogs with liver lesions the reporting veterinarian said that at the time of administration the health status of these dogs was good in 50 of those 65, fair in 13, and unknown in two; 47 of these dogs died.

(Slide.)

Of the dogs with SGPT/ALT elevations, 50 of them did not receive a concomitant drug or vaccination, 112 of them did, and the concomitant status for these 30 is unknown. Of the dogs with liver lesions, 13 did not have concomitant drugs or vaccines and 44 had concomitance. The concomitant status for eight dogs is not known.

(Slide.)

Onset times for liver problems may be seen in the first three months after an insult. Here you see an interesting distribution pattern for these liver enzyme elevations represented in the light green of the bar charts. There is what may be an acute process after administration with episodes corresponding to rising or peak serum levels at up to 14 days. Then you get a second set of what may be

more latent reactions at one to three months after the administration. The onset times for the liver lesions is more difficult to interpret because of course with these lesions the onset time is considered to be the time that the lesion is -- that the biopsy or the histopath tissues are taken. And so it is difficult of course to retroactively decide when the actual onset was, but these are the times that they were determined.

(Slide.)

Another serious concern has been the number of dogs with hematologic or blood-related problems. Thrombocytopenia or low platelet count and anemia or red blood cell count were among the most commonly reported hematologic signs. In dogs low platelet count is frequently caused by the destruction of platelets by an immune response. Immune-mediated hemolytic anemia represented here as IMHA is a life-threatening condition that occurs with an immune response causes the destruction of red blood cells. Again, the assessments for these two problems in dogs receiving ProHeart 6 during the first three years of its approval exceed the assessments for all the other monthly heartworm preventatives combined for all marketed use. For low platelets there were 124 assessments for ProHeart 6, 86 for the other heartworm preventives. For hemolytic anemia

there were 67 assessments for ProHeart 6 and 51 for all the other preventives.

(Slide.)

The onset times for low platelets were similar to those for hemolytic anemia; 43 percent of the low platelets, represented here by the dark-brown bar graph, occurred between one week and one month following the ProHeart 6 administration. Approximately one-half of the hemolytic anemias, represented by the lighter-brown bar graph, occurred between one week and one month following the ProHeart 6 administration.

(Slide.)

For the 124 episodes of low platelets, the reporting veterinarians indicated that at the time of ProHeart 6 administration the health status of the dogs was good in 91, fair in 28, and poor in four. The health status for the dog in that one episode is not known; 45 of these 124 dogs died. For the 67 dogs with hemolytic anemia, the reporting veterinarians indicated their health status was good at the time of administration for 56 of them, fair in 10, and poor in one; 34 of these 67 dogs died.

(Slide.)

Looking at the concomitant status of the dogs with low platelets, in 26 episodes no concomitants were

given. In 76 episodes concomitant drugs or vaccines were given, and the concomitant status for 22 episodes is not known. Of the dogs with hemolytic anemia, 19 did not have concomitant drugs or vaccines, 34 did, and the concomitant status for 14 is unknown.

(Slide.)

I have outlined for you several categories of striking debilitating effects that we have assessed as being possibly associated with the administration of ProHeart 6 such as anaphylactoid reactions, convulsions, low platelets, hemolytic anemia, elevation of liver enzymes and the emergence of liver lesions. They are strongly associated with ProHeart 6 administration by their timing. These are the effects that have driven our concerns.

Dr. Post described the regulatory history of ProHeart 6 showing that the Center for Veterinary Medicine recognized problems and met with the sponsor about them. Label changes, "Dear Doctor" letters, and client information sheets were established. But despite these efforts, we have not seen an appreciable decrease in the numbers of reports received or of serious reactions if you will look at each marketed year from 2001, 2002, 2003, and 2004. The number of deaths possibly or probably related to ProHeart 6 has increased each year since the product was marketed

(Slide.)

The number of assessments for anaphylactoid reactions has decreased since the June, 2002 label change, but it still remains relatively high. The number of assessments for convulsions as we look at each marketed year is not appreciably different. The assessments for the other clinical manifestations involving liver changes and low platelets have increased over time. The assessments for hemolytic anemia appear to be unchanged over the past year.

(Slide.)

The sponsor of an animal drug product has the responsibility to demonstrate that the product is safe and effective prior to approval, but due to the limited size and controlled nature of pre-marketing studies only the most common adverse drug events are known before a new animal drug is marketed. The Center for Veterinary Medicine has a post-marketing system to detect adverse drug events that occur after marketing and when an animal drug is used in a larger and more diverse population. If we determine that a marketed animal drug is likely to be causing serious adverse drug effects, we must take action to prevent additional harm to the animals receiving the product.

(Slide.)

The frequency of ProHeart 6 adverse events,

the severity of these events, which include death, and the temporal association with the administration of ProHeart 6 correlating with established serum levels in dogs that are n good health at the time of administration all raise serious questions about the safety of this product. In working with Fort Dodge Animal Health to address the adverse events associated with ProHeart 6, the Center for Veterinary Medicine has requested three label revisions. Despite these changes, we have continued to receive a large number of serious adverse drug events related to ProHeart 6.

(Slide.)

ProHeart 6 is used to prevent disease in healthy dogs. The adverse drug events associated with ProHeart 6 are particularly striking when compared to other marketed heartworm preventive products. These other products have been on the market longer and have fewer reported serious adverse effects. These are the reasons that led the Center for Veterinary Medicine to request that Fort Dodge Animal Health stop marketing this product until we are satisfied that ProHeart 6 can be safely used in dogs.

Fort Dodge Animal Health will now have the opportunity to present their information on ProHeart 6. I would like to ask you to keep several points in mind while listening to their presentation.

(Slide.)

First of all, the toxicology data presented in Fort Dodge's narrative refers to the oral route of administration. Fort Dodge makes the statement that the toxicological profile of the oral route is relevant to the other routes of administration because of limited metabolism and the long terminal half life. But considering the large numbers of allergic assessments after injection and the possible association with immune-mediated diseases such as low platelets and hemolytic anemia seen in the post-marketing period, this is no longer an assumption that can be made.

(Slide.)

Fort Dodge's narrative states "Approximately 18 million doses of ProHeart 6 have been sold, with more than 12 million doses administered." Fort Dodge calculated reporting rates by taking the number of reports, divided by an estimate of doses sold to veterinarians for the same period. Well, this is problematic because only two-thirds of the doses sold were actually administered, and the doses were not necessarily administered in the same quarter in which they were sold. Also, a dose administered is an estimated dose. It is based on the average number of doses in a vial. Now if one practice sees many small dogs and

another one sees many large dogs, then one will have many more doses in a vial compared to the other. That might all even out in the wash, but it is still just a guesstimate.

It is also important to point out that the numbers calculated by Fort Dodge represent reporting rates, not incidence rates, and that a decline in reported events over time does not necessarily mean a decline in incidence. Reporting of adverse events is usually highest when the product is first marketed and declines over time, sometimes referred to as the Weber Effect.

(Slide.)

According to the Fort Dodge narrative, there were 1.26 allergy event reports per 10,000 doses sold. This reporting rate is two-and-a-half times higher than for Rabvac 3, Fort Dodges rabies vaccine, and 3.1 times higher than for Duramune Max 5L, their distemper-parvo-lepto combination vaccine. Additionally it is mentioned that only 37 percent of these allergy event reports had concomitant vaccine, meaning 63 percent did not have any other reason to react.

Of course many of us are not comfortable in the first place with comparing of biological products such as a vaccine that is supposed to stimulate the immune system, and that might just be expected to result in

allergic reactions, with a drug that has an entirely different purpose and mode of action for which we are not expecting allergic reactions at all. Keep in mind the label clearly states in well-controlled clinical studies ProHeart 6 was safely used in conjunction with a variety of veterinary products including vaccines, anthelmintics, anti-parasitics, antibiotics, analgesics, steroids, non-steroidal anti-inflammatory drugs, anesthetics and flea control products.

(Slide.)

According to the Fort Dodge narrative, there were 1.19 non-allergy event reports per 10,000 doses sold. This reporting rate is four times higher than for Duramune Max and 3.4 times higher than for Rabvac 3; 42 percent of these dogs had concomitant vaccines, leaving us with 58 percent that did not have any other known reason to react.

(Slide.)

Fort Dodge's narrative states "The adverse event case fatality rate associated with ProHeart 6 reports is lower than many Fort Dodge Animal Health harmaceuticals and similar to case fatality rates for the Fort Dodge Animal Health canine vaccine product lines, including Duramune Max 5/4L. Thus the incidence of death does not appear to be causally related to ProHeart 6 usage." Now this is a

difficult connection to make. What are these other Fort Dodge Animal Health pharmaceuticals, and under what circumstances are they be used? What is their target population? Are they injectables? If so, are they anesthetic agents such as Ketaset and Telazol? Are they non-steroidal anti-inflammatories like Ketofen? Does this included euthanasia products like Sleepaway? And how do case fatality rates for Fort Dodge vaccines compare to those for other manufacturers? That information is simply not available. We just cannot make this kind of statement.

(Slide.)

On page 49 of their narrative, Fort Dodge explains how it evaluated adverse event reports by body system, and this is a schematic based on the narrative. All the events were assigned to the medical association category of possible as a starting point. Events considered not likely to be associated with ProHeart 6 were excluded over here as unlikely. The possible group was further reviewed to distinguish between events that were potentially or probably related to specific body systems. The probable group included only those clinical signs that have a reasonable probability of being related to that body system. Events classified as allergic were excluded from the probable group. For neurologic, hematologic and hepatic

cases, only those in the probable category were submitted by Fort Dodge to the highly-esteemed experts for review.

I find this description thoroughly confusing. What is the formalized process for deciding on the categories of unlikely, possible, potential, probable? What is the standardized process for determining which reports go into which categories? What happens with signs like fever or death that aren't associated with any one body system? This all seems highly selective and very subjective. Furthermore, only those in this probable group are included in the calculated reaction rates. It is especially hard to understand why all the cases considered as allergic defined by Fort Dodge as those occurring with the first 48 hours of administration seem to have been excluded from the probable category. Is not the large number of allergic reactions to say nothing of the possibility of subsequent lasting after-effects one of our primary concerns?

(Slide.)

Finally we come to analysis from Banfield, the pet hospital. At first sight you may be impressed by the thought of the wealth of data here for the mining; more than 700,000 doses of ProHeart 6 administered across the country, over eight million patient records available for analysis. But as always, the analysis is really dependent

on the study design. One significant problem is selection bias. Fort Dodge Animal Health compares the number of events that occur among dogs that receive ProHeart 6 here, dogs that received an oral heartworm preventive one or an oral heartworm preventive two, and dogs that received no heartworm preventives at the time of their office visit. Keep that in mind. Both with and without the concomitant administration of vaccines.

Now you will notice that there are more than 5.5 million office visits where dogs received no heartworm preventives. Right away you know that many of these dogs must actually be on heartworm preventive of some kind. It just was not dispensed at that visit. Many owners buy six months supplies or even 12 months at a time. Many owners buy their supplies online or from catalog companies. Perhaps some of these dogs received ProHeart 6 a couple of months before their owners decided to go to Banfield. Also the dogs are not randomly allocated to these different treatment groups, and there is no evidence that these different groups of dogs are comparable, particularly with respect to health status. In fact, there is evidence to the contrary. The adverse event rate was highest for dogs that did not receive a heartworm preventive or a vaccine. And might the health status of these dogs be skewed by

participation in the Banfield Wellness Plan? So these are not in fact a control group, and neither can they be used as a normal baseline for incidence of background effect.

Now what about just comparing the different heartworm products? ProHeart 6 has a market share of about 24 percent in the United States. Among the heartworm preventive encounters at Banfield, 63 percent of them involve ProHeart 6. Consider also that dogs that received heartworm preventive one and two, the oral forms, may have been in poorer health to begin with than those that received ProHeart 6. The ProHeart 6 label states use with caution in sick, debilitated or underweight animals. Furthermore, in this study Fort Dodge assumed that these oral monthly heartworm preventives were administered on the same day that they were dispensed. They concluded that this assumption would result in an underestimate of adverse events. However the opposite may well be true. An owner that brings a sick dog into Banfield for treatment may also purchase a refill of their monthly heartworm medication during that same encounter.

Information bias or observation bias is defined as a flaw in measuring exposure or outcome data that results in different quality or accuracy of information between two comparison groups. It arises from a systematic

difference in the way that exposure or outcome is measured between compared groups. Well, we have already seen how exposure was assessed different, injection of one drug versus oral administration

or, excuse me, purchase perhaps, not necessarily administration that same day of another, versus none dispensed or injected at that particular visit. Another big limitation of this retrospective study is the follow-up of cases. Fort Dodge indicates that each encounter was evaluated for potential adverse events over the following 30 days. However, Fort Dodge does not state how follow-up was done and whether follow-up was similar among these different treatment groups.

Now Banfield has a quality assurance team, and I understand they make follow-up telephone calls after a pet has left their care. But does that continue for 30 days? What if the pet is fine at the three-day callback, but has a problem at day 15 and the owner just doesn't report it? We all know how frustrating it is to think a pet is doing well because the owner hasn't brought him in, and then we find out, oh, they didn't think it was something we should be troubled with, or they tried something suggested by the attendant at the health food store, or they couldn't afford care at the time, or even that they were so upset

with the treatment they received that they went somewhere else. Often when there is an after-hours emergency it is the emergency clinic staff that handles the diagnosis and the referral. Owners may be so upset and angry they never come back to their primary veterinarian. We may never find out what happened until we send that annual checkup reminder for the second or the third time; and of course there may be people who use Banfield for wellcare like vaccines and heartworm preventive, and use another veterinarian for more serious issues. Without an established, consistent method of follow-up for all patients you cannot say a reaction didn't happen just because the owner didn't come in.

Thank you very much for the attention you have given me today, and I will ask you to please keep these points in mind as you now turn that same attention to the representatives from Fort Dodge Animal Health.

MS. SINDELAR: Thank you, Margarita. We are moving along very well. Why don't we take a break now until 10 a.m. If you all will please reconvene at 10 a.m. in the room. Thank you.

(Whereupon, a brief break was taken.)

DR. SUNDLOF: Okay. We are missing our chair. Oh, there he is. Okay. We will reconvene, and you have heard from the Center for Veterinary Medicine. Now it

is my pleasure to have speakers from Fort Dodge Animal Health present their interpretation of the data. So we will go through these presentations and then hopefully we will have a little time, approximately a half-hour before lunch, so that we can start the discussion. We will ask the Advisory Committee to begin the discussion. You are free to ask any of the speakers any questions that you want clarification on, and then after lunch we will begin again. So the first speaker is Dr. Cobb from Fort Dodge.

## ProHeart 6 ADEs/FDAH

**Dr. Rami Cobb**

DR. COBB: Good morning. My name is Rami Cobb. I am Vice President for Pharmaceutical Research and Development at Fort Dodge Animal Health, and I would like to thank the panel and I would like to thank the FDA for the opportunity for us to present the data which support the safety of ProHeart 6.

(Slide.)

Very quickly, moxidectin is the active ingredient in this product. It is a macrocyclic lactone and it is widely used in veterinary medicine as an antiparasitic for horses, dogs, cattle, sheep, swine, and a number of minor species in more than 70 countries around the world. This compound is also in co-development with the World

Health Organization for control of river blindness, onchocerciasis, in humans.

(Slide.)

It is an innovative product in that a single dose provides six months of protection from heartworm disease called by Dirofilaria immitis. In addition, it treats existing hookworms in treated dogs and it brings a singular advantage of overcoming the compliance failures that do exist when monthly products have to be administered to dogs by their owners.

(Slide.)

Reference has been made to the toxicology package which supports ProHeart 6. This is a very extensive toxicology package because this product is approved for use in food-producing animals. In addition to the core tox package, we have recently completely 60 receptor screens that showed no adverse potential for pharmacologic or toxicologic effects, and the data from these screens will be submitted to their CVM for the review as soon as the report is written. In terms of the relevance of the toxicology studies, we have studies of up to two years duration in mice and rats and of one year in dogs. There were no target organs in these studies. There were no histologic or biochemical effects on any organ system. So when we

consider the relevance of these oral toxicology studies to blood levels obtained from injection of ProHeart 6, we find that the exposure of dogs to moxidectin in these studies was 454-fold higher than would be obtained from being given two doses of ProHeart 6 over a one-year period. The two-year carcinogenicity studies showed no increase in tumors.

(Slide.)

In addition to the toxicology, we have conducted a large number of clinical safety studies. These studies demonstrate that the product, the formulated product ProHeart 6, has a wide margin of safety. It is safe to use in breeding animals, both female and male, and it is safe to use in unique canine populations such as ivermectin-sensitive
breeds of dogs and heartworm-positive dogs. In all of these studies at the commercial dose rate of ProHeart 6 there was 100 percent efficacy in controlling heartworm infection, and this occurred not just in laboratory strains of dogs, but in studies with a large number of breeds and crossbred dogs. In the US studies alone, a total of 770 dogs were evaluated, and there were additional studies conducted in international markets.

(Slide.)

If we look at the factors that limit

heartworm control in US dogs, we find that information can be difficult, but I would reference an American Heartworm Society survey conducted in 2001 which found that despite the widespread availability of monthly heartworm preventives there had not been a change in the infection rate of dogs with heartworm in the past 10 years. Some 240,000 dogs were reported testing for heartworm in the United States in 2001. In another survey of dog owners, one-fifth of the dog owners surveyed had missed giving one or more doses of a monthly product to their dogs and had stopped giving oral preventives altogether.

(Slide.)

If we look at our field experience with ProHeart 6, it has been approved and marketed in many countries where heartworm is endemic. The approval in the United States was in June, 2001, and I have listed the other countries where this product is approved and sold. In Australia a similar product, ProHeart SR 12, was approved in October, 2000. This product is used in dogs to provide 12 continuous months of protection against heartworm since the heartworm transmission season there is 12 months long. This product is administered to dogs and is three times the ProHeart 6 dose.

(Slide.)

Our experience with this product has been that there was rapid and broad acceptance by dog owners and veterinary professionals of these products. In the United States the product achieved 24 percent market share and in Australia 47 percent market share.

(Slide.)

If we look at that evolution we find that ProHeart 6 has shown a steady increase in acceptance from launch until the time of its removal from the US market, and similarly in Australia. This is in the face of either steady or declining usage of the monthly products. Almost half of all dogs in Australia that received preventives for heartworm are protected by ProHeart.

(Slide.)

If we look at our adverse event reporting experience recognizing all the deficiencies that go with passive reporting systems, we find that in Australia we, too, have sold significant numbers of doses. Something in excess of 2.2 million doses have been sold in Australia, and I have listed there for you the adverse event reporting rates split out by allergy and by death, areas that were classed as significant by the CVM. The reporting system in Australia is very similar to that in the US. It relies on voluntary reporting by veterinarians, pet owners and the

public, and mandatory reporting by companies.

(Slide.)

In September, 2004, Fort Dodge announced a voluntary recall of ProHeart 6 based on CVM's expressed concerns about the adverse events. These data, we obviously notified the regulatory agencies of other countries where these products are sold, and data were reviewed by the Canadian, Australian, European, and Japanese regulatory authorities. They reviewed not only their own country's post-marketing experience. They also reviewed the US post-marketing experience, and all of these countries confirmed our authorization to continue marketing the product.

(Slide.)

I would like to introduce the two speakers we will have to present our case, and I believe that they will certainly address all of the questions that have been raised by the CVM. Firstly, Dr. Larry Glickman from Purdue University. I think he is known to many of you through his publications. He is he professor of epidemiology and head of the section of clinical epidemiology at Purdue's School of Veterinary Medicine. He is a veterinarian and a Ph.D. in epidemiology. He is also the recipient of many awards and honors, and I would like to just highlight several of those. The Merck Award for Creative in Veterinary Education, the

Pfizer Research Award, the AKC Award for Outstanding Canine Research, and the Outstanding Alumni Award from the University of Pennsylvania. Dr. Glickman comes with excellent credentials.

He conducted a landmark epidemiological survey from a large independent nationwide database, and I want to express my thanks to Banfield, The Pet Hospital, for making that database available for the study, and it covers almost seven million encounters of office visits by dogs to veterinarians. The study evaluated ProHeart 6, two heartworm preventives and vaccines. The results of the study demonstrate no clinically significant increase in adverse events following ProHeart 6 treatment, and that the ProHeart 6 safety profile is similar to that of two monthly heartworm preventives.

Our second speaker is Dr. David Hustead of Fort Dodge Animal Health. In addition to working for Fort Dodge, Dr. Hustead is a member of the VICH Expert Working Group on Pharmacovigilance and is qualified to speak to this issue.

We did conduct a re-review of our database for adverse event reports following the September recall. In this we were assisted by independent experts with expertise in particular areas such as liver, hematology, and

neoplasia. Our conclusions following this review are that the overall reporting rate for ProHeart 6 is low. The reporting rate is declining, and we will specifically address that. Most adverse events appear to be allergic, mild, and self-limiting, that the assignment causality is confounded by concurrent vaccinations, and there is a very varied database of non-allergic adverse event reactions with no pattern that reflect diseases that are commonly seen in dogs.

So thank you. I would like to welcome our first speaker, Dr. Glickman.

## A Controlled Epidemiological Study: The Safety Profile of ProHeart 6 and Two Monthly Heartworm Preventives in Dogs

**Dr. Larry Glickman**

DR. GLICKMAN: Thank you, Rami. I would like to take this opportunity to present to you the results of the controlled epidemiologic study that we conducted. We call it "The Safety Profile of ProHeart 6 and Two Monthly Heartworm Preventives in Dogs." Now as Rami says, it used the large Banfield database and support for development of the database to do this kind of study has been received from Fort Dodge Animal Health, the Centers for Disease Control, Center for Infectious Diseases, and the Food and Drug Administration Center for Veterinary Medicine. This report

will summarize the experience of approximately 900 Banfield veterinarians nationwide who at the time we did the study had administered greater than 700,000 doses of ProHeart 6 to dogs. Banfield practices are -- emphasize preventive medicine, and they are evidence based. Many of their dog owners do belong to the
Wellness Program, which then covers examinations, parasite testing twice a year.

(Slide.)

There are now over 400 Banfield hospitals located in 43 states in the United States, making them very representative geographically. All these hospitals follow similar protocols in the diagnosis, prevention, and treatment of illness. All drugs and vaccines are thoroughly evaluated by Banfield committees before they are adopted and used.

(Slide.)

Now what are some of the advantages of using a large database like this? You have heard from previous speakers the disadvantages of just receiving unfiltered passive reports about adverse events. So what advantage does using this database bring for post-marketing surveillance? First of all, Banfield veterinarians serve two percent or more of the US dog population and is

certainly representative with respect to breed and geography. What is really important to epidemiologic studies is all their medical records are standardized. They are computerized, and they are stored electrically in a central data warehouse. They do routine quality assurance of these records, and all dogs that died routinely review the case records to try and determine causality. You heard before that passive reporting lacks good numerators and good denominators. We think we have both. Good denominators because there is more complete ascertainment of adverse events, follow-up calls are made to all clients after each visit, and since all drugs and vaccines are warranted by the company owners are more likely to return if a problem arises or they perceive a problem.

(Slide.)

Now we were not selective in how we chose the Banfield dogs to include in this study. We took all dog encounters or dog visits over a two-year period from January 1st, 2002, to August 31st, '04, when the drug was voluntarily recalled. Each encounter was evaluated for potential adverse events over the subsequent 30 days, and I would like to emphasize all follow-ups were done the same way regardless of what drug or other treatment the animal may have received. We divided these office visits or

encounters into whether the animal, the dog, had received ProHeart or not, whether they got one of two monthly heartworm preventives which we are going to call heartworm one and heartworm two, whether they were vaccinated or not, or whether they received none of these products. We then calculated adverse events per 10,000 dog visit or encounters, and because of this I will explain in a few minutes the follow-ups weren't necessarily exactly 30 days. For example, when an animal dies. We also calculated the adverse event rate per 10,000 days at risk.

As has been alluded to previously, there are potentially many confounding factors when doing adverse event studies. Other drugs to be given, vaccines to be given. Dogs could have been treated with drugs for other reasons, for example steroidal anti-inflammatories. We took this into account in our final analysis by taking all these potential confounding factors into account.

(Slide.)

Now this first slide actually was shown to you earlier this morning. We looked at a total of almost seven million encounters over this two-year period of time. We broke these encounters down into whether the dogs had received ProHeart or not, heartworm preventive one or not, heartworm preventive two or not, or no treatment. That

included then all dogs seen at Banfield. Within each of those categories we subdivided them into whether they had received a vaccine or not, and that is shown on the website of this slide.

Now I would like to point out some interesting highlights here for you. You see three sets of numbers under each drug. For example, you see a large N, which are number of encounters in which that drug was given. So for ProHeart it would be a total of 735,000-plus. For heartworm preventive one vaccine, yes/no, heartworm preventive two vaccine, yes/no, and you also see then the number of animals in the category, the number of dogs. That's the N. The NA is the number of adverse events, and the rate which is the second column divided by the first column. So we are looking at incidence rates. We are not just counting events, and several things are striking from this.

First of all, if you look at the ProHeart and the heartworm one or the heartworm two, and they are in yellow there, if you look at the rates you can see that when animals receive this product, any of these products without vaccine, the rates are remarkably similar; 89.2 for ProHeart, 89.1 for heartworm preventive one, and 70 for heartworm preventive two. Now the rates are higher in the

last group, the animals that received no heartworm treatment, because those are probably sicker animals coming to the hospital for diagnosis. So for completeness we include them, but they are not really our primary comparison group. We are comparing events between the three heartworm preventives.

Within each of the heartworm preventive categories you can see if you look at vaccine yes and vaccine no there are approximately twice as many dogs that receive vaccine at the same time they receive ProHeart. Same for heartworm preventive two, approximately twice as many were vaccinated as not vaccinated, and the same for heartworm preventive two. Why is this important? Because we know vaccines are associated with adverse events themselves, and so you cannot ignore this heavy use of vaccine at the same time these preventives are given. Otherwise you get a biased outcome.

(Slide.)

Now this shows the use by Banfield veterinarians over time of ProHeart 6. There are two lines on the graph. The upper are dotted lines. It shows the number of animals that received ProHeart with vaccine. The bottom solid line are the number of dogs that had ProHeart without vaccine, and you can see it is roughly a two-to-one

ratio there. You can also see the seasonal pattern in the use of ProHeart with the peaks occurring each year during the peak of mosquito activity, usually from about April or May through September. The third thing is obvious that over this period of time there was increased use of ProHeart by Banfield veterinarians.

(Slide.)

I would like to walk you through our initial analysis where we looked at and calculated adverse event rates for animals receiving each of these products or divided into these eight groups. These eight groups are shown on the left. As we said, there are four possibilities -- ProHeart, heartworm one, heartworm two, or any vaccine -- and we show you then in the top row the animals that received none of these, and so there are no Ys in those boxes. The next one would be animals that received any vaccine, so it would have a Y under a vaccine, and then further down you see each of the heartworm preventives, both alone and with a vaccine. We looked at a variety of potential associated adverse event types. They are shown across the top: liver disease, neurologic disease, ocular disease, immune-mediated disease, and allergic reactions.

First let me focus your attention on ocular disease, for which there was a very low rate of adverse

events. Overall if you look in the any row, the bottom row, there was only 0.3 per 10,000 ocular events, and so it was hard to distinguish between drug types. For neurologic disease the rate was higher overall, 6.1, and the rates were fairly consistent between the three heartworm preventives. Immune-mediated the same, the overall rate is 5.1, and the comparisons between the three heartworm products did not point out any major differences. Allergic reactions are very interesting, and I will talk to them in a separate slide shortly. I would like to focus your attention here to liver disease, where if you look at the top row these are the animals we expected to be the sickest, and they had the highest adverse event rate per 10,000 at 61.6. If you look at vaccine alone, which would be the second row, the rate is 35.0. Then if you look at the three heartworm products going down with or without vaccine, you can see the rates are fairly similar. But in this analysis, which was unadjusted for any potential confounders like age or weight or use of other drugs like steroids, the ProHeart group, especially with vaccine, has the highest rate at 41.6 per 10,000.

(Slide.)

Now as I said, we also looked at adverse events when calculated per 10,000 days of risk. Why did we

do this? Because the way we follow it up in animals, an animal following a drug administration, for example ProHeart 6, we looked over the next 30 days to see if they had any adverse events. If they had for example an adverse liver event we counted that and then kept looking over the remaining part of the 39 days. However, if they are in the 30-day period an animal had received a vaccine -- let's say on day 14 following ProHeart, we would stop the follow-up with ProHeart at day 14 and then start a new 30-day follow-up associated with the vaccine. As a result, not all of the follow-up periods for all the products were exactly the same. In fact, they were slightly longer for ProHeart 6. Therefore, the importance of adjusting our rates per 10,000 days at risk, and if you look at this graph then you can see that the adverse event rate for the oral monthly heartworm preventives being 1.15 and 0.79 are not too different from what you see for ProHeart 6 when adjusting for days at risk. Again, the animals that received none had the highest rate, which we expected.

(Slide.)

Now let's look at some other potential adverse events in the same way. We have looked at death, cancer, cardiovascular disease and anaphylaxis. Now the rates for both -- for anaphylaxis were extremely low, a

total of 0.5 per 10,000, and were not very different between the products. The cardiovascular disease rate was slightly higher, overall 16.6, but also not different between the two monthlies and the ProHeart.

There are some striking findings though with respect to what we all agree is the most serious adverse outcome, which is death. When you look at the overall death rate, the last row under death and under rate, you can see that rate is 116.2 per 10,000. Then when you look further up now and look at the different products, the heartworm products of vaccines, you see that they are very similar except for one product. Heartworm one when given without any vaccine, the adverse event rate was the highest at 22.0 per 10,000.

The cancer rates I am going speak to separately. They also seem not to be similar between the groups in that the adverse event rates, meaning cancer, are slightly higher for the ProHeart 6 group both with and without vaccine, 6.1 and 4.2 per 10,000. We are going to get back to this and look at it in more detail.

Now I said I was going to get back to the allergic reactions because we've never had data like this to look at in terms of what products are associated with what reactions. But we look at the second row down, which is

vaccine, only vaccine, the adverse event rate was 44.3 per 10,000. But if you then look at heartworm two alone, heartworm one alone, or ProHeart alone, you get 51.8, 14.3, 54.3. Very similar but slightly higher than what we see for vaccine. So that was for the products given with vaccine.

When you look at the products give alone, heartworm two alone the rate is 18.7, heartworm one alone allergic reaction is 14.3, and ProHeart alone 18.4. Here we can really see the impact of vaccine when given with a heartworm product. It increased the rate by about two-and-a-half fold, once again suggesting you cannot ignore administration of concurrent vaccine with heartworm preventives when you are looking at adverse event reports.

(Slide.)

Once again to adjust for differences in the length of follow-up, this shows the relative rates of allergic reactions per 10,000, and you can see heartworm one, heartworm two, and ProHeart 6 are very comparable with vaccines clearly having the highest risk of allergic events.

(Slide.)

Now I said I would come back to cancer. We looked at three cancers -- lymphosarcoma, histiocytoma, and mast cell tumors -- because these are very common tumors in dogs, and previously we saw that ProHeart might be

associated with a high risk of cancer. Well, in fact, that increased risk is only found with mast cell tumor. If you look at the adverse event rate for heartworm one only it is 0.024, whereas for ProHeart 6 it is 0.072. So the important point here is the absolute rates are extremely small, but there is a slight increase with ProHeart 6 when it comes to mast cell tumor and it is also higher than you see with vaccine, but again the absolute difference is very small.

(Slide.)

As I said, it is important to adjust the potential confounding factors like age, like weight, when you are looking at the effects of the three heartworm preventives, and that is what we did in each of these models. So the results I am showing you are fully adjusted for everything else that we looked at, and the ones that I am going to show you are the only ones that came out statistically significant at P less than 0.05. So in the adverse event model for liver disease, which this one is, steroids increase the risk of liver disease by 25 percent. Which is not a surprising finding knowing what we do about the effect of steroids on the liver. In this fully-adjusted model now, ProHeart 6 is not associated with an increased risk of liver adverse events. Matter of fact, it suggests a decreased risk, and each additional dose of ProHeart given

further decreases the risk by eight percent. Now the reason this may be a little misleading is because of the bottom entry there. You see interaction of Proheart 6 and age, and the high significance level suggests that age is modifying the effect of ProHeart in terms of adverse events regarding the liver.

(Slide.)

So we plotted out what the age effect is. So on the X axis you see age in years, Y axis is the risk of liver disease, and you can see there is a relations. It is a straight line. But in dogs less than four years of age ProHeart is actually associated with a decreased risk of liver disease, while with older dogs, older than four, it is associated with an increased risk. But the overall net effect is no increased risk.

(Slide.)

Now we built a similar model for allergic reactions. We can go over this quickly because ProHeart, heartworm, and vaccine -- and this is heartworm one -- appear to all increase the risk of allergic reactions consistent with the previous findings. But vaccine has by far the greatest effect, increasing risk of allergic events by 151 percent. Now the two anti-inflammatory classes, non-steroidals and steroidals, also increased the risk of

allergic events, but it was theorized we are pretty sure this happens because steroids are actually used to treat allergic events. Once again each additional dose of ProHeart is actually a decreased risk of liver events. That is important. So the more ProHeart you give, you would not expect to see an increase in allergic event, but actually a decrease.

(Slide.)

Now this is the adjusted model looking at the adverse events associated for cancer. Lymphosarcoma and histiocytoma, there were no relationships between risk for those cancers and any of the heartworm preventive products. Steroids still increase the risk of lymphosarcoma, but that is because it is used to treat lymphosarcoma. Now with mast cell tumor we did confirm a slightly increased risk associated for ProHeart use, increased by 27 percent, and a very unexpected finding was an increased risk of mast cell tumor associated with non-steroidal anti-inflammatory use, and we need to explore this further.

(Slide.)

Of course death certainly is the most severe reaction, and in this fully-adjusted model heartworm one, the most commonly used monthly oral, appeared to increase the risk of death by 23 percent. Whereas ProHeart actually

decreased the risk by 71 percent, and each additional ProHeart further decreased the risk of death by nine percent.

(Slide.)

So what do we conclude from these analyses? I concluded that the safety profile of ProHeart is similar to two monthly heartworm preventives, the two orals, with two exceptions. One, there is an up-to-now biologically unexplained but very small increased risk of mast cell tumor following ProHeart 6 administration. Perhaps more important is the 23 percent increased risk of death following the use of the most common monthly heartworm preventive. In our study that is heartworm one. The other thing I think it is important to realize is that the adverse events probably were underestimated for the monthly heartworm preventative versus the injectables. Why? Because veterinarians are more likely to observe an adverse event when they give the product and the animal is actually in the office, whereas they are less likely to observe adverse events when the drug is given at home by the owner. Also we know and we have heard that many owners don't administer the oral medications when they are supposed to, and yet we are counting adverse events as if they were given. So again we are going to underestimate the rates with these products.

(Slide.)

I want to emphasize that these epidemiologic analyses adjusted for effects of concurrent vaccination and other potential confounding factors of which we found several, and it is hard to interpret results of adverse events without adjusting for these. Unlike passive reporting systems that are unable to calculate incidence rates, we can calculate incidence rates, and as important we can compare these incidence rates between the heartworm products. We utilize recorded medical events and not unfiltered reports from veterinarians or owners. We know there are biases associated with reports from owners and veterinarians, and certainly unreporting. We don't have that problem with our database. This database gave us an opportunity to test causal hypotheses that were generated through the FDA CVM passive reporting system, and I think this is the appropriate use of epidemiology, both in human medicine and veterinary medicine.

(Slide.)

My final conclusion, and I believe this based on the results I showed you and based on results I have not shown you for lack of time, that the safety profile of ProHeart 6 in controlled epidemiologic studies was definitely favorable compared with two monthly heartworm

preventatives. My own conclusion is that there appears to be no scientific rationale for the continued withdrawal of ProHeart 6 from the marketplace. Thank you.

## FDAH Adverse Event Report Re-Analysis

**Dr. David Hustead**

DR. HUSTEAD: My name is Dave Hustead. I am a Senior Director at Fort Dodge Animal Health. My areas of responsibility are technical and regulatory affairs. I am going to present to you today a re-analysis of ProHeart 6 adverse events.

Before I start my prepared presentation though, I have been asked by the FDA to offer a subtle correction to Dr. Post's presentation. Dr. Post did show you a very nice three-line graph with three different colors for the numbers of adverse drug experience reports received by the CVM. While the graph he presented was correct, his verbal description of the legends for the three lines was incorrect. So we would ask that you look at that graph carefully and interpret it appropriately. The graph does show that the number of initial adverse drug experience reports are declining to the CVM.

(Slide.)

At Fort Dodge Animal Health our Professional Services Department is responsible for adverse event

investigations. They are also responsible for the regulatory compliance associated with those investigations. They have additional responsibilities in technical support and professional customer service. We have 28 veterinarians in our Professional Services Department. They have extensive practical clinical experience prior to joining industry. In addition, we have three PhDs and seven veterinary technicians.

(Slide.)

All reports of suspected adverse events are investigated by Fort Dodge Animal Health staff. To improve the quality of the data that we collect during those investigations, Fort Dodge Animal Health routinely pays for diagnostic services, including referrals to specialists. All reports received, regardless of causality and regardless of scientific plausibility, are recorded and submitted to the CVM per our regulations 21 CFR Chapter 514.8.

(Slide.)

To add in the analysis of adverse event reports, Fort Dodge places those reports into four categories. Those categories are injection site reports, allergy reports, non-allergic systemic reports, and lack of efficacy reports.

(Slide.)

We conduct medical association assessments based on VICH-approved draft guidelines. VICH is an international group of regulators and industry attempting to standardize and harmonize the differing regulations involved with adverse event reporting. I am proud to be a member of that group. As recommended by VICH, Fort Dodge Animal Health assesses each event as a whole. This is in contrast to the CVM practice of assessing each causality assessment individually and in isolation. We use three categories of the VICH system: possible, unlikely, and probable. All events are placed into the possible category. Possible means that the drug of concern is one of equally plausible explanations.

(Slide.)

If during our investigation we obtain sufficient information to determine that the event is not likely to be associated with the product or there are other more plausible explanations, the event is then placed in the unlikely association category. For an event to be placed in the association probable category all the following must be met. There must be a reasonable association in time; the adverse event should be reasonable given what is known about the pharmacology of the drug and the toxicology of the drug; and there should be no other equally plausible explanations.

(Slide.)

Now the CVM has said to you that ProHeart 6 has a very large number of adverse event reports associated with this use, and that this number of adverse event reports compares very unfavorably to monthly heartworm preventatives, and that this then supports a conclusion about the safety performance of ProHeart 6. Fort Dodge Animal Health believes that to make valid comparisons between products you must resolve a host of data inconsistencies, and often these comparisons are difficult if not impossible. Two primary areas of data inconsistencies are in the products themselves and then the users' expectations of those products, and then of the differing adverse event collection systems used to record adverse events for the different products. Product differences with ProHeart 6 as compared to monthly preventatives are that most monthly preventatives are given at home as a treat. There is a common belief among owners that medications given at home in this manner are not really drugs. If they are not really drugs then adverse clinical signs which are seen in the post-administration period may draw no association from the owner to product administration. If no association to the product is ever made, then no adverse event report is created. These

products, the monthly preventatives, are rarely given by veterinarians, and they are rarely given in conjunction with injectable products. These products have radically different sales, and sales differences do impact the numbers of adverse event reports which are received. Finally, the differing companies in this instance have differing adverse event collection systems. These systems collect, investigate, quantify, and then submit adverse event reports differently, and this creates substantial bias within the datasets for review. Unless these differing issues can be resolved, valid conclusions and comparisons are difficult if not impossible.

(Slide.)

ProHeart 6 has a substantial over-reporting bias associated with its use as compared to monthly heartworm preventatives, and these over-reporting biases become extremely valid if what you want to do is compare the rate of reporting of one product to another. ProHeart 6 is an innovative, sustained-released product. It was recently released on the marketplace. Early in its use veterinarians lacked an effective frame of reference to make reasonable conclusions about clinical signs they see in the post-administration period, drawing questions as to whether those clinical signs are or are not due to the drug which they

have just given. These questions then stimulate calls to our Customer Service Department because they know there is a wide range of veterinarians there with expertise to answer their questions. The product is a sustained-release drug. It is now plausible for a veterinarian to think that a set of clinical signs they see months post-administration just might be related to products used, again generating a call to the company.

Concurrent use with vaccine is common. Dr. Glickman has shown to you that vaccine use dramatically impacts adverse event reports. The CVM considers these events where ProHeart 6 and vaccine were used together as ProHeart 6 adverse events with concomitant vaccine use. It is equally valid to say the event is a vaccine adverse event with ProHeart 6 concomitant use. ProHeart 6 is injected by veterinarians. Injected drugs are viewed as powerful medications by the users and the clients. Veterinarians know exactly when the product was given because such is documented in the patient's record. If the animal subsequently has signs, the veterinarian easily sees in his record when ProHeart 6 was given.

Fort Dodge Animal Health has sent out two "Dear Doctor" letters during the time the product was on the market. These discussed safety issues associated with the

product. It is not unreasonable to think that these letters have created a bias amongst veterinarians to be concerned about clinical signs they would see in the post-administration period. Finally, there have been a large number and widely disseminated news reports and website postings critical of ProHeart 6. I can assure you if the veterinarians themselves have not seen these their clients have, and they have drawn these to the attention of their veterinarian. Clearly ProHeart 6 is subject to reporting biases that would not apply to monthly heartworm preventative products.

(Slide.)

Let me give you an example of how this over-reporting bias works. The practitioner is presented with a dog who has anemia and lethargy. When presented with a diagnostic dilemma the veterinarian will ask the owner questions about the dog's medical history. It is my experience based on decades now of adverse event reporting that veterinarians don't ask "When was your dog given his last heartworm preventative?" If this question is never asked then the veterinarian never draws an association to the clinical signs they are observing and the product that was given in the previous period. If they don't make that connection and adverse event report is never generated.

ProHeart 6 is very different. The veterinarian knows when ProHeart was given. He is then very likely to make a temporal association between the use of the product and the clinical signs being seen. As we have an effective Technical Services Department, this leads to a telephone call which basically goes, "This is what I've seen. What you guys think?" At that instant an adverse event report has been created, and that adverse event report, regardless of what we find in our investigation, will be submitted to the CVM.

(Slide.)

We believe we need to take a much closer look at the numbers of adverse event reports that the CVM has presented to you, and especially as how they compare the monthly heartworm preventatives to ProHeart 6. This is information that Fort Dodge was able to obtain from the CVM based on the Freedom of Information request. This is information not freely available. What I want you to see is to look carefully at the year 2003 and compare it to 2002, and notice for the monthly heartworm preventatives there is a dramatic increase in reporting between 2002 and 2003. Now Fort Dodge is not going to speculate about why this change exists. It is not germane to the issue that we have come here to discuss today, but it is important for you to notice

the difference in the pattern of reporting. It is also important for you to know that we have reviewed the pattern of reporting prior to 2001, and the low level that is seen in 2001 and 2002 continues in the previous history of these products.

Based on this data, Fort Dodge believes that it is inappropriate to sum the number of adverse event reports for the monthly heartworm preventatives and to conclude that the low number of adverse event reports associated with those monthly preventatives somehow supports a conclusion about the safety of ProHeart 6. It is very much apples and oranges. We believe that the differences in the numbers of adverse event reports much more clearly are an effect of the system involved in reporting those adverse event reports than the biological behavior of any of the products.

I would now draw your attention to the ProHeart 6 adverse event numbers. In 2001 we had 677 adverse event reports. This is a relatively low number compared to 2002, but this is completely explainable as the launch of ProHeart 6 was in June of 2001, well past when most veterinarians are administering their annually-based heartworm preventative programs. So therefore the amount of ProHeart 6 that was actually used in dogs in 2001 is

relatively small. 2002 was the first year where we had the product on the market for a full heartworm season, and so we saw a large increase in the amount of product use. This brings about an increase in adverse event reports, as would be expected. In 2003 you will notice that this number drops, and we believe this is important and significant as veterinarians grow accustomed to products the adverse event reports typically do drop.

In addition, we would like to draw your attention to the market share information provided in the final column. This is Fort Dodge's best estimate of the relative market shares of these three products, and this information is obtained from an outside source. If you assume for just a moment that all three of these products have the exact same biological behavior, and if you assume for the moment that all three products have identical adverse event reporting systems, then you would assume that the number of adverse event reports would follow the ranks that the products are sold in the marketplace. This is exactly what you see. The product with the highest market share has the highest number of adverse event reports. The product with the lowest market share has the lowest number of adverse event reports, and the product in the middle is in the middle for the number of adverse event reports.

(Slide.)

This is the same information which I just provided, but it excludes inefficacy reports. In general when we are using passive surveillance systems you have two issues that you are interested in. One is safety. The other is efficacy. If your question is safety then it is more important to drop out the lack of efficacy reports so you can just look at those reports which imply a safety concern about the product. I will not go into detail in looking at this slide because what you need to know is everything I told you about the previous slide applies to this slide as well. Therefore, Fort Dodge concludes that the number of adverse event reports associated with ProHeart 6 in 2003 compares favorably to other heartworm preventative products, and that any comparison of adverse event numbers from periods before 2003 is inaccurate.

(Slide.)

This is the number of adverse event reports that Fort Dodge Animal Health has received associated with ProHeart 6 from launch to recall by quarter. There are just a few interesting take-home messages here. You will see a peak in the second and third quarters of the year 2002. This is with the same peak that I showed you in adverse event reporting numbers in the graph that I just showed you.

This is certainly to be expected. You will also notice that there are three peaks in this graph, each of them associated with the second and third quarter of each year. This corresponds to increased use of the product in the spring and summer as would be expected with a heartworm preventative in the United States. You should also notice that these peaks go down each year with subsequent use of the product. We believe these decreased are significant.

(Slide.)

Now we do use reporting rates as an analysis tool. We believe that while these are not perfect assessments, they do offer some advantages to just looking at gross reporting numbers. The primary problem with gross reporting numbers is that they fail to provide any estimate at all of an incidence rate. We completely agree that reporting rates are not incidence rates. No one has ever made such a claim. In addition, gross numbers fail to account for changes in products used, and so reporting rates are a valuable tool as long as you understand what they are and you understand their deficiencies. Reporting rates are calculated by dividing the number of adverse event reports you get by the doses of product which are sold in that same period of time.

(Slide.)

This is the same data that I showed you in the previous graph looking at gross numbers of adverse event reports, but corrected for reporting rate. What you see here again is the peak in 2002. I have addressed this. The reason for the rise in the numerator number that represents this peak. But the reason this peak is so high in this analysis is because the denominator number or the sales number has been artificially reduced. The reason for that artificial reduction is that as I said before ProHeart 6 was launched late in 2001. We sold a lot of product in 2001 that didn't get used. That product was then used in 2002. If the product is used in 2002 but not sold in 2002 then it doesn't get into the 2002 calculation. In addition, much of the product that we sold in 2001 was short dated. This required veterinarians to return the product to us in exchange for product with better dating. These exchanges don't show up in our sales figures. So therefore the large peak here in incidence rate is an artificial elevation based on increasing numbers of adverse event report rates, balanced off at actual decreases in sales when looked at in this analysis method. After the peak, though, that is seen in 2002, you will notice that the product rapidly falls and establishes a steady stayed graph, which is what we expect when we look at incidence rates calculations over time.

The annualized reporting rate of ProHeart 6 in June, 2001, through May, 2002, was 2.45 reports for 10,000 doses sold. For the next calendar year, June, '02 to June, '03, it's 4.3 per 10,000 doses sold. But following that period it then reduces to 2.13 for 10,000 doses sold. It is clear that looking at ProHeart 6 either from a reporting numbers standpoint or a reporting rate standpoint that following a peak in early 2002 that the reporting for ProHeart 6 is decreasing.

(Slide.)

The CVM has previously presented to you that there are 485 deaths which are at least possibly related to ProHeart 6 and that this number compares very unfavorably to the numbers of death which have been associated with other monthly heartworm preventative products. I have addressed earlier in my presentation the reasons why these comparisons are inappropriate. They are inappropriate for total numbers of adverse event reports as they are inappropriate for the numbers of death. There are no differences.

There are additional issues, though, with the numbers, with the death reports that we would like to discuss with you. Fort Dodge was able to obtain 353 adverse event reports from the CVM from a Freedom of Information request. We then took a look at those causality assessments

conducted by the CVM and simply graphed them on a chart.

(Slide.)

You will see that five percent of the death reports have been characterized by the CVM as probably related to ProHeart 6. This compares to 77 percent of those assessments which are possibly related to ProHeart 6. There has been some indication this morning that the Kramer Modified Algorithm is an unbiased and objective way to review causality assessments. This is not the opinion of the VICH Working Group. They don't think -- the do not recommend the Kramer assessment to be used. In addition, while the Kramer system appears to be unbiased and objective, we believe -- I believe that is because it produces a number, and we as people are always predisposed to treat numbers as an objective and unbiased assessment of something. But if you look at the Kramer Algorithm what you see is that each of its components asks an extremely subjective question subject to all sorts of biases. A question like "Were there other reasonable alternative candidates?" Well, whether there are other reasonable alternative candidates depends on how far you look. So these are subjective questions producing an objective answer.

We would like to point out that the single

highest category of assessments on this graph is the zero causality score. It compromises -- or comprises, excuse me, 37 percent of the causality assessments given. If during the causality assessment conducted by the CVM if just one of the questions in the causality component scoring had come up with one less number in it, all of those causality assessments would have fallen to the other side of that black line, and now suddenly 55 percent of the adverse event reports are now remotely associated with ProHeart 6.

(Slide.)

So to summarize, the CVM themselves have assessed five percent of these events as probable -- these death reports as probably related to ProHeart 6. The CVM has assessed 77 percent of them to be possibly related to ProHeart 6. We would ask should all of these greater than possibly assessed adverse events be treated equally in an analysis of the safety performance of the product? We would say the answer to that is no. Also we would ask should market withdrawals be supported on events whose assessments are possibly related to ProHeart 6.

(Slide.)

Fort Dodge Animal Health believes there are other significant issues involved with the death assessments which have been performed by the CVM. From our review of

the cases that we have been able to look at closely, we believe there is a large number of scientifically implausible cases still within the clinical assessments of possible or above. These begin with concurrent vaccination. It is my opinion that when vaccines and ProHeart 6 is given that any assessment to which product is causality associated with the product is impossible. There are events in the database where cancers have been reported in patients, and these cancers have been reported less than six weeks after ProHeart 6 administration. We believe there is no scientific data to support the speculation that a medically-reasonable product can be given to a patient and induce clinically-observable cancers in less than six weeks.

I have already discussed with you the reasons for being concerned about causality assessments of zero. If these events are not removed from the database, any conclusion about the seriousness of ProHeart 6 based on the numbers of death reports is an exaggeration.

(Slide.)

Additionally, we have concerns simply about how the causality assessments were done all by themselves. Fort Dodge Animal Health again has reviewed a subset of the death events it could get. We reviewed 29. In one-third of these events we found that the FDA had assessed the death as

possibly related to ProHeart 6. Fort Dodge Animal Health using the Kramer scoring system as the CVM recommends assessed these events are remotely related to ProHeart 6.

Let me give you two examples. A dog with a hemorrhagic episode is presented a few days after administration of ProHeart 6. The dog dies. An necropsy is conducted. During the analysis of the information clinically significant levels of rat poison are found in the dog's liver. All this information is provided to the CVM, but regardless they score the case as possibly related to ProHeart 6.

Another case, a dog is presented with pain its abdomen four months after administration of ProHeart 6. The dog dies. A necropsy is conducted. A hemangiosarcoma is found in the dog's liver. This information is provided to the CVM. Regardless, this case is assessed as probably related to ProHeart 5.

MR. : --- five minutes.

DR. HUSTEAD: Yes. Thank you.

(Slide.)

We believe that the numbers of death reports need to be placed in their proper context. Even if you take the number of adverse -- of deaths associated with adverse events which the CVM has stated, which is approximately 500,

you need to compare that rate of dating with the expected mortality rate in a large number of dogs. If you do the math on the 500 assessments of the CVM divided by the number of dogs exposed over time, you will see that approximately 20 dogs per million have been reported associated with death associated with the use of ProHeart 6. The obvious question is what is the mortality rate in the canine population. I wish I knew. We have scoured the literature to try to determine what the established amount of death and mortality is in dogs, but we don't know. Various sources give various different information. We believe that very conservatively we have assessed this to be five percent. We would point out that a peer-reviewed journal article will show up in the peer-reviewed press very quickly showing that this rate is actually eight percent.

If you use five percent as your assessment and divide that by time, you will find that if you give any medication at all to one million dogs that approximately 50,000 of those dogs would be expected to die over the next one year. What we are saying here is that the numbers of death reports associated with ProHeart 6 when looked at amongst the numbers of dogs which have been presented, that rate cannot be extracted from the background of mortality in the dog population.

(Slide.)

Fort Dodge does place its adverse event reports into categories. Two of those categories are allergic reports and non-allergic systemic reports. Our allergic category are the largest events that we see, but only slightly thus so. The signs in this category are typical for what you would expect in a dog with allergy occurring within 48 hours. The systemic non-allergy reports involve any body system that is not typical of an allergy. We would point out that many of the events in this category overlap into the allergic category, but they are just not stereotypical enough to be called allergy.

(Slide.)

The rate of adverse reporting with allergy is low at the rate that has been previously told to you at 1.26 reports per 10,000 doses sold. The vast majority of 80 percent of these events are self-limiting and the dog does return to normal. The relative frequency of these allergy events are decreasing over time with no breed predilection. We have stated that the rate of these reports is similar. We have never said that they are identical, and what we have said is that given the limitations in the systems, trying to measure biologically complicated systems, these reporting rates are similar to Fort Dodge Animal Health vaccines.

(Slide.)

Now the CVM has expressed to you a concern about some unknown toxic mechanism that seems to be involving a wide variety of systemic responses in the dog. We believe that it is widely recognized that when an approved medicinal product causes toxicity that this toxicity would be expected to be seen in a small number of target organs. In contrast, the wide variety of suspected adverse event syndromes assigned to ProHeart 6 by the CVM is consistent with these standards.

(Slide.)

Fort Dodge has conducted a complete re-analysis of all of its non-allergy adverse event reports. To assist us in this analysis we did obtain the expertise of outside consultants who are extremely well recognized. We had the neurological cases reviewed by Dr. DeLahunta, Diplomat of Internal Medicine, specialty in neurology. The hepatic and hematologic events were reviewed by Dr. Alan Rebar, Diplomat of Veterinary Pathologists with a specialty in clinical pathology. The neoplasia cases were reviewed by Dr. Phillip Bergman, Diplomat of American College of Internal Medicine, specialty in oncology.

(Slide.)

It is the opinion of these independent

experts and Fort Dodge Animal Health that the majority of the adverse events are not causally related to ProHeart 6 and reflect the normal range of diseases occurring in the dog population.

(Slide.)

To summarize, Moxidectin-based products are used in a variety of animal species in over 70 countries around the world. There is an extensive toxicology study conducted in mice, rats, and dogs to support the approval of moxidectin for use in food animals, and this food animal approval is important. The food animal, the regulations to get a food animal drug approved are much higher than a domestic animal. So therefore the amount of information we have associated with moxidectin use in animals is much higher than would be associated with most domestic animal approvals. I have three more slides.

In a one-year dog toxicology study, the daily dose of moxidectin resulting in a monthly moxidectin exposure that is 454 times greater than the doses administered that are recommended with ProHeart 6 resulted in no toxicologically-significant findings.

(Slide.)

The rate of submission of initial adverse drug experience reports to the CVM has decreased in 2002 and

-- excuse me, 2003 and 2004 as compared to 2002. ProHeart 6 is subjected to substantial over-reporting bias. Even with this over-reporting bias and when corrected for market share, the numbers of adverse events associated with ProHeart 6 is similar to major competitors.

DR. CRAIGMILL: Dr. Hustead, I am very sorry, but we are out of time. You have exhausted your hour plus a few minutes and we must move on. If you could skip to your last slides please very quickly. Most people on the panel have the handouts and can review them.

DR. HUSTEAD: My last slide is based on this analysis. Fort Dodge Animal Health concludes that ProHeart 6 is a safe and effective product for prevention of canine heartworm disease.

DR. SUNDLOF: Okay. We are skipping ahead in our agenda to a clarification of VMAC questions, and at this time we are going to ask the VMAC committee members to ask questions of any of the speakers that have presented today and begin the discussion. I am going to ask Dr. Dan McChesney who is our Director of the Office of Surveillance and Compliance in CVM to go over the questions which we will ask for a committee response to later on this afternoon. Dr. McChesney.

## **Clarification of VMAC Questions**

DR. McCHESNEY: Thank you. As you can see up on the slide there, we have really two questions. The first question we would like to ask the committee is "Based on the presentations and information provided, is ProHeart 6 safe for use in dogs?" We would like a yes or no answer to that. We would also like to know, "If there are remaining safety concerns with ProHeart 6, what additional avenues of research could be explored to mitigate and/or prevent the adverse events?" So we would believe there should be discussion on that. Thank you, and turn it over to the committee now.

DR. CRAIGMILL: Thank you very much. With that I would like to open up for questions from the committee to the people who have made presentations this morning. Lauren.

DR. TREPANIER: I have a question for Dr. Glickman. I would like better clarification of the way the Banfield study was done. I'm not really clear on how the adverse event was defined and what time frame. It says 30 days, but in what time frame were clients called? That seems a little unclear to me.

DR. GLICKMAN: Okay. As part of normal -- maybe I will let someone from Banfield address the question

of when are clients called first before then I will answer your question.

DR. CAMPBELL: I'm Scott Campbell. I'm a veterinarian ---.

(Adjusting equipment.)

DR. CAMPBELL: Okay. My name is Scott Campbell. I'm a veterinarian and CEO of Banfield, and what we do is we call all of our clients three days after they have been in the hospital. We also cover reactions at no cost to the clients, and they get a warranty when they leave that says that. So they all know that, and our clients on average come in about three-and-a-half times a year. So we see them very, very frequently, and of our clients about 94 percent come back for all their future care and service. So whenever we get a reaction we are very confident we get it reported because we pay for it, and that is one of the reasons we do it, because we want our patients to get the very best care.

DR. TREPANIER: Are you open for emergencies?

DR. CAMPBELL: Most of our hospitals are open seven days a week and we refer. We have relationships with emergency clinics, you know, in the area, and then those clinics of course refer back to us in the morning, or at least we get the report and any reports are followed up on

by telephone that day.

DR. TREPANIER: But if a patient was seen in an emergency clinic that wasn't associated with Banfield you wouldn't necessarily know about it?

DR. CAMPBELL: I suppose it's possible, but emergency clinics generally -- you know, we have a relationship with a clinic that we refer to, and we give the clients the number of that emergency clinic when we are not closed. Those clinics, you know, prepare a report for us the next day.

DR. GLICKMAN: I will answer the second part then. I believe it was how do we define adverse events? Is that the second part? What we did is we looked at the list of adverse events that had been reported on the website from FDA CVM and reports that Fort Dodge has received. Then we classified them into neurologic disease, liver disease, et cetera. Mostly it is by system and also allergic reactions and anaphylaxis. Then we go to experts in the field and say what would constitute a legitimate or accurate diagnosis, and we go into the database then from Banfield and pull out all the codes. The consist primarily of two types, clinically diagnosed abnormalities, like hepatitis, and then laboratory abnormalities. In the case of liver disease it would consist of three enzymes and bilirubin, and so we look

for abnormalities in laboratory values, clinical diagnosis, and in different combinations of the two.

MS. : A slide is up there is you want to.

DR. GLICKMAN: Okay. There's a slide. This is actually -- it was too busy to show, but it's a detailed breakdown for each class of adverse event, what went into defining an animal with that event.

DR. TREPANIER: So how does the diagnosis get coded? So let's say an animal is seen and then a week later calls and speaks to a veterinarian and the animal is vomiting. Does that get coded as a diagnosis in the record, or is it only a diagnosis if it gets coded associated with a visit?

DR. GLICKMAN: No, it can get coded either way. It gets into the medical record either as a code if there is a corresponding code in the Banfield database or as medical notes, which are also computerized and are searched. So we can do it either way, but it does get into the record when it is reported back to the Banfield clinic.

DR. MEALEY: Thank you. Going back to -- this is for you again, Dr. Glickman.

DR. GLICKMAN: Good.

DR. MEALEY: You had a slide up there and the

slides in here, I didn't think I was getting old, but I couldn't see the print in here. So I am going back to the original that you guys sent us. For anaphylaxis, you know, you broke down allergic reactions and things like that, but for anaphylaxis you didn't further break down the rates of ProHeart, you know, with vaccine, and heartworm one with and without vaccine. And I think if I remember right, your conclusion was that the rate was low for anaphylaxis?

DR. GLICKMAN: Yes. The rates as we showed, overall rate, was 0.5 per 10,000 for anaphylaxis, and the rates then within the different categories, the highest one was actually 1.7, which would have been heartworm preventive two with the vaccine. The rest were somewhat lower for the other products without vaccine.

DR. MEALEY: But if you look at the heartworm preventives alone -- tell me if I am looking at this correctly. ProHeart by itself was more than twice -- had more than twice the rate of anaphylaxis than any of the other heartworm preventives, is that correct?

DR. GLICKMAN: That's correct. The 0.7 versus roughly 0.2, and when we looked at those -- and I didn't show you all the models we developed. When we looked at the risk factors or the associated factors for anaphylaxis they do not come out. None of the heartworm

preventive products come out in the multivariant models. That is why there was no multivariant model to show with significant findings, and because the rates are so low those models are more unstable than would be the models for let's say liver events, which are more common. But we didn't find any significant risk effects for any of the heartworm products for anaphylaxis.

DR. MEALEY: Okay. Thank you.

DR. McGLONE: Dr. Glickman, you are very popular today. I was struck by the difference in the rate of death of dogs in the FDA data and in your model, and also in the raw data it appeared that there were -- it was a higher rate of death among dogs vaccinated and treated with the product in question. But in your multivariant model near the end of your presentation, the risk for death was actually decreased. So I am wondering what was in that multivariant model that accounted for the differences that when they weren't in the model.

DR. GLICKMAN: Right. I don't remember specifically for that model, but we did further analysis of every model. We put all potential interactions into the model, all potential two-way interactions, and the variable that seemed to have the greatest impact on most of these models in terms of changing the appearance from the initial

analysis to the adjusted was age of the animal. For example, we know that liver disease and death are highly correlated with age. The older the animal, the more likely they are to experience this. So in answer in general, age appeared to be the largest confounding factor. That is why I would almost rather rely rather on the absolute rates, the adjusted models, to come up with the true independent impact of these products.

DR. McGLONE: Right. Were any of the variables in model correlated with heartworm use, and were they also included?

DR. GLICKMAN: Yes. All the variant models --

DR. McGLONE: Heartworm medication.

DR. GLICKMAN: Yeah. I mean frequency of use or what product is used. We tried to look at the factors that could be either associated with the use or the product or the adverse events we were looking at and put them in the model, and not discriminate and actually put them in all models. There are a lot of relationships between the variables in the models like age and weight obviously and those things, and you can't anticipate all of them. It's nice we have the luxury with such a large data set to be able to put all the potential confounders in the model and

still come up with stable estimates, and that's what we've done.

DR. McGLONE: But doesn't including correlated variables remove the effect of the correlated variable? In other words, if the product is given more to older dogs than younger dogs for example, and then age is in the model, then doesn't the age effect sort of seem to account for the effect that might also be the product?

DR. GLICKMAN: It is a little more -- that is true, but it's a little more complicated because for age to be a confounder in one of these looking for associations it would have to be both associated with the use of the product, but also associated with the outcome that you are looking at.

DR. McGLONE: Well, age would be a --.

DR. GLICKMAN: And age is, yeah. It's just the most obvious one. But then of course age and weight are highly correlated in these databases.

DR. McGLONE: Thank you.

DR. LUSTER: I had a couple of clarifications, one for Dr. Brown and one for Dr. Glickman. On the FDA data, does the anaphylactic responses that are measured, are the reported? Maybe I missed the data, but I saw that you look at concomitants with all disease, but is

there concomitant vaccination data particularly with anaphylaxis that you have available? And secondly, do you have any data that would suggest that ProHeart 6 is used when anaphylaxis is observed which seems to be very high incidence that there is -- that that occurs after the first use or after multiple uses?

DR. CRAIGMILL: Dr. Luster, is that a question for Dr. Brown?

DR. LUSTER: Dr. Brown, yeah.

DR. BROWN: I'm not sure that I heard the first part of the question. I'm sorry. If you --

DR. LUSTER: Okay. The first question was whether the data from the ADEs indicated that there was concomitant, specifically concomitant vaccination with the anaphylactic responses.

DR. BROWN: Yes. We have for the anaphylactic reactions that approximately half or a little less than half of them also had concomitant vaccinations with drugs.

DR. LUSTER: Okay. You mentioned that with the whole, all the pathologies. Is that specifically for vaccination for anaphylaxis as well?

DR. BROWN: It would not necessarily be only vaccinations. It could be some other injection or tablet at

the same time.

DR. LUSTER: So you don't have that information then. Do you have information on the incidence of anaphylaxis -- not the incidence, but when anaphylaxis occurs whether it is after the initial first time the drug is used or after multiple uses with ProHeart?

DR. BROWN: There are instances were a dog might not react with the first injection of ProHeart 6, but subsequently have a reaction after say the second or the third. It seems that those reactions tend to be more involving say the liver signs or sometimes possibly the hemolytic anemias. In other words, there wouldn't necessarily be a full-blown anaphylactoid reaction, but could include some of those other signs as well. Typically if there were an anaphylactoid reaction the first time you wouldn't get a subsequent injection, but there are dogs that have had two or three, or some of them more than that, injections of ProHeart 6 and we are not seeing the reactions until say the fourth injection.

DR. CRAIGMILL: Essentially your ADEs do distinguish that?

DR. BROWN: Yes, they do. We do write that down in reports and take a look at that.

DR. CRAIGMILL: And one quick question for

Dr. Glickman. I was a little confused on how does diagnosis differentiate between anaphylaxis, allergy, and immune-medicated specifically?

DR. GLICKMAN: I think I'll pass that question on to Dr. --- perhaps or Will.

DR. NOVAK: So could you repeat the question?

DR. CRAIGMILL: What are the specific differences in the diagnosis between immune-mediated, allergy, and anaphylaxis?

DR. NOVAK: As far as the database system we would look for both anything that is clinical signs as well as any laboratory findings that are tracked. And so as far as what Dr. Glickman's work did on analyzing all of that, he was -- my understanding is that he was searching through the database for anything that was in the medical notes as well as any laboratory findings as well as any clinical signs that were associated. Is that correct, Larry?

DR. GLICKMAN: Yes. We really only used medical notes as backup. So it was not part of our original search. But codes are up here. The actual codes that were used to describe each of those. Now if you are asking how does the clinician distinguish when they write down auto-immune hemolytic anemia, that would be based on Banfield

diagnostic protocols. They do have protocols that they shared with me for an auto-immune hemolytic anemia.

DR. CRAIGMILL: I am still a little confused, because I mean an immune hemolytic anemia would be relatively straightforward diagnosis, but allergy, I am not sure what that might -- how that was specifically addressed.

DR. GLICKMAN: Okay. That is a good question. I said we used medical notes as a backup. So for example when there was a diagnosis of allergic event vaccine associate or allergic event drug associated, we took a sample, a very large subsample of the medical notes to go in and characterize what they are calling the allergic events, and it parallels what you see in the veterinary textbook as a description of allergy. Facial swelling, pruritus, urticaria, and vomiting were the major ones.

DR. NELSON: A different avenue I want to approach here. In the paper that we got from Fort Dodge there are talking about the heartworm-positive dogs in trials, and on page 26 there were two safety studies that are quoted and one of these -- well, first of all, are these experimentally-infected animals or naturally-infected animals?

DR. COBB: There were two types of studies conducted, one in which heartworm-positive dogs were

determined by circulating microfilaria. There was a second study that was conducted at the request of the Center that involved implanting adult heartworms into the dog so that the actual age of the adult heartworm was known and when the infection was established was known. So there were two types of studies done.

DR. NELSON: So one experimental and one naturally infected?

DR. COBB: Right.

DR. NELSON: Okay. The other thing, on page 22 when you were testing for efficacy against three- and four-month-old heartworms there is talk about now effective it is. There weren't any reactions noted during that time period on the three-month and four-month-old heartworms.

DR. COBB: I would ask Dr. Rock to comment on that one.

DR. ROCK: My name is David Rock. I am Director of New Product Development for Fort Dodge Animal Health, and could I just hear the question one more time as far as the three- and four-month infection retroactive studies?

DR. NELSON: Right. On page 22 of your report there is talk about the efficacy against three- and four-month-old heartworms post-infection.

DR. ROCK: Correct.

DR. NELSON: The question is was there any reactions noted when this was -- when the drug was given to these dogs? It talks about efficacy but nothing about any reactions.

DR. ROCK: Okay. There were no adverse reactions to the dogs. There was no adulticidal activity of the drug in those experiments. You will see that these worms were classified as abnormal but still alive. So the rate of kill again as an adulticide was not very fast and did not cause an adverse reaction, no.

DR. NELSON: Next one. When you were testing the product, because -- you know, partly the heartworm label was added later about, you know, if adverse effects were seen in heartworm-positive dogs. And just from, you know, kind of doing some review, you know, Veterinarians VIN, we see some Veterinarians Report no cases, and some veterinarians report multiple cases. Has anybody tested or seen what happens to this product, you know, just for example theoretically, if a technician drew it up with the 18 or 20 gauge but then try to force it through a 22 gauge needle? Do the microspheres break up? Would it cause an increased dosage of moxidectin release, or has that even been looked at?

DR. COBB: What we do see, the product is designed to go through a 21 gauge needle or larger. What can happen if you use a finer gauge needle is that sometimes you may get a blockage in the needle and the product is difficult to force through. That is the only information I can provide you. It is impossible to push them through very, very fine needles because they are particles that are suspended in the carrier.

DR. NELSON: Now if the product sits like where you have from the time it is mixed up there is, what, a 30-day? If it sits for two months is the moxidectin released in the vehicle?

DR. COBB: We have tested this quite extensively after three months post-reconstitution, and moxidectin is not significantly acceleratedly released upon storage. The vehicle is specifically designed to maintain suspension of the microspheres and it does not draw out the moxidectin selectively. So we do recommend that the product is used only with the appropriate vehicle. It should not be resuspended in saline for example where the microspheres could settle fairly quickly.

DR. NELSON: One other thing I noticed in reviewing the 36 cases that were given to us by the CVM, about 22 of those 36 cases there was no heartworm status

provided, whether they were negative, positive. Any previous heartworm preventative, one particular dog had had one injection, two years later had another injection, but no mention of what was given in between or any preventive history.

DR. HUSTEAD: That is a reflection of the data that you can get from veterinarians. You can ask the questions and you get the answers that you get. We recognize the deficiency in the information.

DR. CRAIGMILL: Dr. Nelson, we can continue this after lunch. I am informed that we must break now. Ms. Sindelar has some information before we do so. We will reconvene at 12:30.

MS. SINDELAR: All right. Thank you very much. There is a restaurant downstairs. There are also local restaurants in the area which you can walk to, and if the members and consultants will stay for just a minute so that we can all have lunch together, and we will reconvene here at 12:30. Thank you.

(Whereupon, a luncheon recess was taken at 11:30 a.m.)

A F T E R N O O N  S E S S I O N

(12:30 p.m.)

MS. SINDELAR: Thank you, everyone. Please take your seats and we will restart the meeting. Because we have so many questions still to the panel members we would

like to continue for the next 30 minutes, from 12:30 until 1:00, entertaining questions to those who have presented today. At 1:00 we will begin with the open public hearing as originally planned. So, Art, you can take it from here. Thank you.

DR. CRAIGMILL: With that I would like to open up questions again for both representatives from CVM and from Fort Dodge. Panel members? Yes, Corrie, Dr. Brown.

DR. C. BROWN: I have a question for Dr. Cobb and Dr. Brown. We heard a lot of numbers this morning about the numbers of animals that were affected by various clinical syndromes and the numbers that died. However I didn't see much in the way of pathologic reports. What is the correlation for instance of 378 dogs with convulsions, 61 died. How many of those was a necropsy performed, and what were the histopathologic findings? I see that there is sort of -- I haven't quite seen a biological correlation between adverse events and death.

DR. BROWN: Let me address that, a portion of that for you. I can't give you any exact consistent type of necropsy finding because necropsies aren't always done. For the necropsies that were done, the reports would vary very much. For example, sometimes you might have

encephalomylacia with hemorrhage in the brain. You might have hemorrhage or lesions in other organs in the body with the comment consistent with anaphylaxis. With some of them the lesions might be consistent with severe protracted seizures. It depended very much on the type of death that occurred.

DR. C. BROWN: So in how many of these 485 deaths do we have necropsy data?

DR. BROWN: I can't say exactly. I would say probably in a third or less.

DR. C. BROWN: Well, a third would be a lot to look at, and that would be very helpful, and we have 192 -- 257 dogs with liver problems; 85 died. Did those 85 die due to liver problems? It is not clear from the report and Dr. Cobb from the Fort Dodge information, all I saw was that there were 15 livers examined histologically. Is that the sum total of what was looked at from your perspective?

DR. COBB: I would like to answer that question in a little bit more detail by asking Dr. Rebar to comment. He did the expert evaluation of all the liver reports that we believed could possibly be related to ProHeart 6, and they did include liver reports that did have either pathology or clinical pathology liver enzyme, and I would ask Dr. Rebar if he would describe what he did.

DR. REBAR: So I will focus specifically on the hepatic adverse event reports.

DR. C. BROWN: Yes. You know, Dr. Rebar, I have read the report so I know about all the -- you know, the liver enzymes. I want to know about the anatomic pathology.

DR. REBAR: Well, in that case I might defer to Keith Harris who actually did the pathology.

(Laughter.)

DR. HARRIS: Thanks. Thanks, Dr. Brown. That is a good question and we did only look at 15 cases, and those were selected based on the cases that we actually felt confident -- were graded as confident that were added cases. We were looking at ones that we were trying to look for a pattern to see if we had a common -- morphologic changes that would suggest a common mechanism for any toxicity we might see. So we selected the more severe cases to look at. You know, it has been brought up before there is not a lot of full post-mortem cases. They weren't done in a systematic way. Some are more thorough than others, but that is the reason we chose this subset.

DR. C. BROWN: Okay. So 485 cases. If you think there are necropsy results on a third, well, that's what, 150? And of that looking at it in this context in a

controlled systematic way, there were a total of 15 livers examined?

DR. HARRIS: That is all we examined that we could identify clear-cut cases with liver signs.

DR. C. BROWN: And CVM didn't consult with any other pathologist to look at this series of cases?

DR. BROWN: The liver lesions that we are looking at are not necessarily of course the same ones that Fort Dodge has looked at, and the pathology reports would have come in from across the country. The reason for pathology, the types of lesions found in histopath are not any one specific type of lesion. They are not all hepaticellular necrosis for example. Some of them could have been that. Some of them could have been consistent with allergic type reactions or hemolytic anemia. It depended very -- we don't have any one consistent type of lesion across the board.

DR. REBAR: Dr. Brown, if I could make one comment that may expands a little bit what Dr. Harris was saying. I actually examined the case studies from about 251 animals, and of those there were 15 that had histopathology of the liver. I think that those were the cadre of 15 that were actually examined by Dr. Harris.

DR. C. BROWN: So no one looked at the

pathology reports with an idea in mind about what moxidectin might cause pathologically?

DR. COBB: We examined all the histopathology reports that were available to us, and they numbered 15. We did ask for them to be looked at by Dr. Harris. In addition, we did identify a number in excess of 200 reports that had diagnoses that were either liver or were hematologic; and for those, although they did not necessarily have histopath reports, they may have had clinical reports, they may have had autopsy reports, and those we referred to Dr. Rebar since he has expertise both on hematology and on liver. So, yes, we made a very extensive effort to evaluate in excess of 250 of those cases that met the case definition of possibly related. Thank you.

DR. CRAIGMILL: Other members of the panel? Yes, please go ahead.

DR. GROSECLOSE: Question for either Dr. Post or Dr. Brown. What is the FDA policy on follow-ups once you receive a report?

DR. BROWN: It is usual for the drug company, the sponsor, to perform follow-ups on adverse events and send them in subsequently to the initial report if there is any further information to be gathered. If we are able to

and we feel that we really need to have further information, we might inquire back to the sponsor if further information is available, and if not could they please find out if it is and if so submit it to us. Sometimes we might call the veterinarian for clarification.

DR. GROSECLOSE: You mentioned that your report mentioned that 99 percent of most adverse events are reported from the sponsor. In this particular case, what was the proportion of adverse events that were reported from the sponsor versus from the general public or veterinarians directly, and did that change over time?

DR. BROWN: I think that with ProHeart 6 as with all the other drugs really the large, the vast majority, are the ones that are submitted by the sponsor. We will have reports also submitted directly from the public, and as you might expect those numbers of reports increase significantly after increased publicity. But we have not included any of the reports coming in from the public since the voluntary recall.

DR. GROSECLOSE: Among the seven veterinarians who review the adverse events, have you ever -- do you do a single classification, or do you have numerous observers classify the cases to see whether different observers would classify them similarly?

DR. BROWN: Usually it is one person doing each report. But if someone is having trouble really trying to understand the information in the medical record or if there are a lot of factors to be considered we might say, "Hey, could you take a look at this report and run it through the algorithm and see what you come up with?"

DR. GROSECLOSE: Okay. Thank you. Dr. Glickman, could you talk a little bit about the risk window that you talked about, and for example if a dog is treated with heartworm preventive there was the three-day follow-up. But when you looked at that dog's experience over time and following the treatment, how long was the typical follow-up to capture any adverse events that might have occurred? And also any treatment, for example the steroids, and how did that enter into your multivariant analysis?

DR. GLICKMAN: Okay. I think there are a couple of questions there. With respect to the callbacks, that was not part of any of our research. That was a normal part of Banfield practice. The information captured from those callbacks gets into the medical record. We go only with what was in the medical record. Our follow-ups were intended to be 30 days for each exposure, whether it was ProHeart or one of the monthlies. Our intent was to follow those animals for 30 days to see what happened in that 30

day window. The only time we cut it short, we would have terminated of course if the animal died, or if during the 30-day window for example an animal that had previously gotten ProHeart and we were following then received a vaccine we would stop the 30-day window with ProHeart at the time of the vaccine and then start a new 30-day period for the vaccine and so on. So it turns out that of course not every animal was followed for 30 days unless they fall in for ProHeart, but the average length of time is 29.2 days. So it is pretty close, and for heartworm one, which is the major product oral, it was 27.2 days. So we are pretty close at 30.

Now you can arbitrarily say 60 days or 90 days. Of course you can get more and more being cut off when you go that far, and it is pretty standard in human vaccine and drug studies to use the 30-day window. Why I am not quite sure. What we do know though from the 30-day window is that the first three days will capture about 90 percent of the allergic reactions. Day seven to about 21 will capture most of the immune-mediated like hemolytic anemia and ITP, and then the other events it is hard to tell. They are scattered throughout the window. So that was our approach. I agree with it could have been 60 days. I certainly wouldn't want it to be less than 30 days for

most of these events.

DR. GROSECLOSE: So any steroids that would have been administered within a 30-day period would have showed up in the model as well, and they may not have been administered at the time of the ProHeart administration.

DR. GLICKMAN: That is correct, and we felt it important to look especially at steroids because of course we have very little quantifiable information about what they do, and for the non-steroidals that is also true as it was up until a little while ago in human medicine. So we felt we had to improve. While we could have picked other classes of drug, you know, where do you stop? So we decided to at least with drugs use the steroidals and the non-steroidals, especially knowing about the effect of the steroidals on the risk of liver disease.

DR. GROSECLOSE: While I am hogging the mic, one question about did you look at the group of dogs that during this time period received only one ProHeart administration versus those who received two or more to see what the model might have looked like in that?

DR. GLICKMAN: Yes. Every time we found a significant relationship between ProHeart and an adverse event we followed up with a days at risk analysis, but we also followed up with a dose response analysis. So we went

back in the record to see whether this was the first, second, third, fourth, fifth time. The most we had was five, but given every six months and we did it for two-and-a-half years, that is all we would expect. So when possible we looked for a dose response relationship. Now a little bit of caution. I mean, it is possible that an animal had gone previously to another vet, a non-Banfield veterinarian, and received ProHeart. We would have not known about that. But, yes, we always look for a dose response relationship and did not find it.

DR. GROSECLOSE: Thank you.

DR. PAPICH: Dr. Brown, when you were talking about the elevations in liver enzymes, are the elevations that are assessed by comparing one measurement to another? Or were these simply liver enzymes that were above normal as a single measurement.

DR. BROWN: These would have been liver enzymes that were above normal as reported by the individual veterinarian according to their laboratories that they used.

DR. PAPICH: So is it possible then that these could have been liver enzymes above normal that the animal had prior to any drug administration?

DR. BROWN: That's always possible. Now sometimes of course we were fortunate and there it was based

on blood work drawn before, and in those circumstances then of course we could assign a higher score.

DR. PAPICH: Relating to the liver enzymes, Dr. Glickman, when you talked about in your evaluation liver disease, are you talking about elevations in liver enzymes or is this documented liver disease in those animals?

DR. GLICKMAN: A comment about liver enzymes first. We had the benefit that Banfield submits virtually all of their laboratory work to one laboratory nationwide, and that is Antech. So that built in some sort of degree of consistency on the results for liver enzymes. We collaborated with Al Rebar to tell us what the conservative cutoff levels are for each enzyme, and in fact originally I just took what was in the Banfield databases as being normal or abnormal. When Dr. Rebar looked at that he says, "No, I'd rather be more conservative and more specific." So he set the enzyme levels. Then what we did was we looked at either any abnormal laboratory value of the enzymes, any clinical diagnosis of liver disease or combinations of those -- meaning having both a clinical and a laboratory finding or either one of those. We looked at it all different ways, and it really didn't change any of the relationships. So we went with what I showed you was primarily a liver disease diagnosis plus a laboratory abnormality.

DR. PAPICH: I would like to ask a couple of questions about the pharmacokinetics of the drug. In this slow-release preparation in the graphs that were shown to us today it shows a peak of about seven to 10 days in the picture that we saw. It is in the handouts that we have. It shows a nice average plasma concentration. For anyone at Fort Dodge that is familiar with the kinetics, I don't know who that would be, if they could answer this. The picture that we have seen representing average concentrations, just how variable are those concentrations? Like what is reality in other words when we talk about a peak of seven to 10 days? Is that highly variable or is that consistent? Can somebody comment about that?

DR. COBB: There is individual dog-to-dog variability, and we did run pharmacokinetic studies in laboratory beagles which generally gave more uniform results than in the crossbred dogs that we looked at. The window of peak blood levels appears to range from about five days to 12 days in individual dogs. We do not see gross, huge variabilities or peaks at 30 days or later. It generally is a pretty indicative value to say that the product peaks between seven and 10 days.

DR. PAPICH: Relating again to the nature of the formulation, could somebody from Fort Dodge fill us in a

little bit about the nature of the formulation? I'm not sure that everybody around the table understands the -- just what makes this formulation slow release versus something else so that we can better understand how this drug is released over such a long period.

DR. COBB: I would be very pleased to answer that, Dr. Papich. It's in two parts. One relates to the inherent characteristics of the molecule. Moxidectin is a very highly

--- molecule with a very long half life in dogs, approximately eight days. So it particularly does lend itself to a sustained release formulation. It also has a very large volume of distribution regardless of whether it is applied topically or orally or by injection. So it penetrates into the fatty tissues of the body. It makes it very suitable for sustained release. We put this molecule into a microsphere that is based on glyceryl tristearate.

So when the product is presented to the veterinarian it comes in two vials. One vial has the microspheres, glyceryl tristearate containing 10 percent moxidectin. The micropheres are manufactured to very, very strict size criteria so that the surface area is very uniform and the release of moxidectin from these microspheres occurs in a very uniform manner. The second

bottle contains the diluent, and the diluent is formulated to a very specific viscosity to maintain the microspheres in suspension after the product is reconstituted. Because in order to get a uniform dose it is very important that the microspheres remain uniformly distributed through that vehicle. So that is just a thumbnail sketch of what the product is and why it does work in the way that it does work.

DR. PAPICH: Are there studies that you have done in dogs where either the diluent and/or the material in he microsphere minus the moxidectin has been injected into dogs?

DR. COBB: We have indeed. In our investigations of allergic events we ran a great many tests looking both at complete product and looking at every component within the product including the preservatives that are used because they are not ---. We were not able to consistently demonstrate allergic reactions in dogs to any of the components or the finished product. We could on occasion by intradermal skin allergy testing see a wheel or a flare with either moxidectin or the moxidectin microsphere, but that was not repeatable and not consistent. We did try to reinduce allergic infection -- reactions in dogs that had reacted to ProHeart.

We were not successful in doing that with either the complete product or with any of the components, and through the University of Wisconsin we ran a large-scale study where more than 7,000 dogs were treated with ProHeart 6. They concurrently received vaccines, either five antigen, seven antigen, or nine antigen parenteral vaccines. They also received kennel cough vaccines, some of which were intranasal and some were parenteral. What we were trying to do was to identify reactive dogs so that we could look at investigating the problem further.

With these 7,000 dogs we were able to identify one dog that showed facial swelling on treatment with ProHeart. We have subsequently retreated that dog twice with ProHeart and have been unable to reproduce any clinical manifestations at all. So it does appear to be idiosyncratic.

DR. PAPICH: Thank you.

DR. RIDDELL: I have got a couple of questions relative to reporting for Dr. Brown, and also a question for Dr. Hustead. Dr. Brown, relative to the suggestion that there is under-reporting, when I looked through the FDA packet all the reference are human. So my questions are what general comments do you have supporting the under-reporting phenomenon, two, specific to ProHeart 6,

and the third, what would be your response to Dr. Hustead's comment that there may actually be over-reporting of ProHeart 6?

DR. BROWN: I think that when we are talking about the reports that come in we have to consider that they come in from the same kinds of people, that is veterinarians and from owners, and they come in from all across the country and they come into the drug companies who then submit them to us. As far as comparing under-reporting in veterinary medicine with under-reporting in human medicine, I don't know that I could make that kind of comparison. I do know that we are far more limited in veterinary medicine as far as being able to have patient information available and to look prospectively particularly at any kinds of reaction to reporting.

With ProHeart6 as far as claiming that that might be over-reported, I think that if you are looking to a relation to media interest and public interest such as the websites for example, those really started to kick in early in the spring of last year. But as you can see from our slides that we've shown you before, we already had a great many reports coming in before any public interest was stimulated.

DR. RIDDELL: Thank you. Dr. Hustead, the

Modified Kramer System may actually have been a benefit for ProHeart 6 because the dechallenge and rechallenge really wouldn't be totaled into the score. But you say with your familiarity with VICH that they don't recommend that system. Does the system that VICH recommends have some added objectivity to it as far as grading adverse events?

DR. HUSTEAD: Let me try to address both your questions about under-reporting and about VICH and the Modified Kramer System. I don't think there is any question that adverse events in general are under-reported. I would think every expert in the world would say that as a general rule of thumb all adverse events are under-reported. The point that I was trying to make is that if you are going to compare two products that you have to look at the relative issues between those two products and determine if the same level of under-reporting exists. It was my point that in a comparison that the reporting biases are different with the two products. So I hope that was clear.

Versus the Modified Kramer System, I think you can argue the advantages and disadvantages of the Kramer System for a couple of days, as you can with the VICH system for a couple of days; and we have done so, haven't we, on VICH? Numerous times. There is no objective information that would say which system is better or not. At the end of

the day, it was VICH's interpretation that both systems are subjective, and that with the Kramer System you get a number and that makes people have some confidence that that's objective. But at the end of the day all you are doing is asking an educated person "Do you think timing is positively or negatively correlated with the event? Do you think the pharmacology and toxicology of the event are positively or negatively associated with the event? Do you think there are alternative explanations positive or negative associated with the event?" And then you make an assessment at the bottom.

DR. RIDDELL: Thank you.

**Open Public Hearing**

**Aleta Sindelar**

DR. CRAIGMILL: Thanks very much keep those questions. We will be coming back. At this time we are gong to move to the public comment section of the program. You are not off the hot seats yet, folks. Lots more to come. Ms. Sindelar will lead this discussion, but before we begin with the public hearing I am going to read this statement into the record about the open public hearing.

"Both the Food and Drug Administration, FDA, and the public believe in a transparent process for information gathering and decision making. To insure such

transparency at the open pubic hearing session of the Advisory Committee meeting FDA believes that it is important to understand the context of an individual's presentation. For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the committee of any financial relationship that you may have with any company or any group that is likely to be impacted by the topic of this meeting. For example, the financial information may include the company's or a group's payment of your travel, lodging, or other expenses in connection with your attendance at the meeting. Likewise, FDA encourages you at the beginning of your statement to advise the Committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking." Ms. Sindelar.

MS. SINDELAR: Thank you very much. To begin the open public hearing let's begin with Tom Stafford. Please remain standing at the mic for your entire presentation, and you have five minutes.

MR. STAFFORD: Well, anyway, I have no financial reason to be here. I'm financially poor. I drove myself from Texas and spent the night in my van. My daughter wrote you all something. I wrote about three or

four different speeches, and after reading hers the night before I left I threw mine away. She was five years old when we got Bear. At his death she was 13. I have a son 17 and a wife.

She starts out, "To the makers of ProHeart 6, to my knowledge my dad and I took our dog, Bear, and our two other dogs, Angel and Mickey, to the vet as we did every year to get a checkup. As my dad waited for the vet to call us in he noticed that they had come out with a new shot, a six-month heartworm shot. So he decided to look into it, asked the vet about it. Everybody thought it was okay, even though Bear had had 15 seizures just three months prior. Three of our other dogs got the same shot on the date of May 9th, 2002. Not two days after that my nine-pound Pekinese had a seizure."

At that point I really thought my kids were overreacting or just looking at the dog seeing our other dog having seizures just -- I didn't believe it to be quite honest until after everything else happened. Anyway, back.

"Poor Bear had his first reported seizure on 11/13 of '01, not long after my dad stayed up all night with Bear watching over him and taking care of him because in the night total Bear had 15 seizures. I woke up the next day to my mom taking me to school, and I come out of my room and

saw that Bear was having another seizure. I was very horrified. I was sad, scared, confused all at once. It hurt me to see him, and I went to school so disturbed I could hardly focus.

"Over a period of time Bear had three more shots of this ProHeart 6 and a lot more seizures, and my family and I helped him through them all. It was really heartbreaking. On the day of September 14, 2004, five months after his last shot, my dad and I had helped him through a little seizure before we left. We put him in a wire cage, kennel-type, very large. We put a blanket in there to comfort him in case he started banging around like he normally does. We went to load some furniture that we had bought. We loaded it, came back home."

She got the keys from me and unlocked the door to the house. "I went inside and looked at Bear. I said after I walked by him putting my stuff down I thought at first my best friend of eight years, long, loving years, was just sleeping. Then I bent down to pet him in his cage calling his name trying to wake him up. After a little while of trying to wake him up I finally realized my best friend in the whole wide world was dead. The look on his face, his teeth were bared, his eyes were wide open. I broke out in tears. Just ran outside hysterical trying to

get it out that Bear was dead. My dad realized what happened, ran inside, a couple of seconds later came out crying. I'll never forget that look in his eyes. I don't think I could ever forget seeing it. That is one of the things. I found him, Bear, myself. I was the one. I'll never love another dog like I loved him and there'll never be another dog like him. He was the sweetest dog you'd ever meet, a 90-pound solid black German Shepherd. He knew when you were upset, and he would always come in my room and whine and sit right down by me, comfort me. He was the best dog ever. Because of the makers of ProHeart 6 I will never see him again."

MS. SINDELAR: Tom, thank you very much for your testimony. Our second speaker is Dr. Scott Campbell.

DR. CAMPBELL: Okay. Thank you very much for giving us the opportunity to speak. My colleagues and I are here today. We are the purchasers of many pharmaceuticals and from many of the folks here in the room, and our practice is a general practice, and so we buy a lot of stuff. Fort Dodge has picked up our hotel bills for being -- as one of the things -- as the only thing for being here.

A couple of things I want to tell about our practice in the next slide. I guess the next slide.

(Slide.)

Our practice is an evidence-based practice. We make all of our decisions based on evidence, and we are continually trying to find new evidence every day. Pets are certainly a part of the family unit for our three-and-a-half million clients, and so that is the standard that we hold ourselves to. Really providing those pets the same care that we want for ourselves. We do that in a lot of different ways, and if we had more time I could go into those. But it is a very high standard that we hold ourselves to.

Products that are on our formulary, our criteria, you know, are many, but certainly the top ones are it has to be safe. That's a go/no-go for us. We believe every product on our formulary is safe, and we'll take it off the formulary immediately if we believe that it's not.

The second thing is, you know, does the patient receive it? You know, is it in a formulation where the client, you know, is actually going to give the medication; and then it has to be effective, and the effectiveness is a combination of how good is the chemical or the molecule as well as is the client going to give it.

We can, you know, certainly show anybody that we have the same case mix as most traditional practices. As I said, 1,016 veterinarians and 443 hospitals.

DR. NOVAK: Next slide.

(Slide.)

I'm Dr. Will Novak. I'm the chief medical officer for Banfield, and one of my responsibilities is managing our surveillance system. This was mentioned earlier. We have a quality assurance team which is about a dozen people that are tracking a number of different things on quality client service, medical records to making sure that the documentation is accurate, and then our surveillance system. So we are tracking the incidence of disease, and we compare that to rate of reactions that may be seen with vaccines, with antibiotics, with any of the drugs. And we are constantly using this to do a national risk assessment on each component of the products that we're using. Next slide.

(Slide.)

So we track medication reaction rate and it is on a national reporting system, and so this is not a passive system. It is an active system. Anytime that there is a report of any problems from a client or it is noted during the healthcare visit that is automatically put into our reporting and tracking system. So that is required as a practice standard. So as such we are constantly reviewing that data, running statistical analysis against it, and the

analysis that we have done has shown that whenever we compare our medical record details back to our reporting system we find that there is a very, very high, statistically-significant correlation. So as such we got a lot of confidence in the information that we've got. Next slide.

(Slide.)

We do approximately 2.7 million doses of vaccine annually, and that rate is going up every year. So one of the things that we believe is that we do have a really good understanding of how preventative care works based on the science of large numbers. All of our vaccines are warranted, including the vaccine reactions as was mentioned earlier today. So that is another reason that we have good information on having really excellent follow-up care when it comes to any patients having problems. Overall reaction rates on our reporting system for anaphylaxis is 1.8 per 10,000 doses, and that is not purchased or delivered. That is what was actually given to the patient. So this is one of the few cases where we have got data that really says what did the patient get, what was the reaction rates that we are seeing. We also have a peer-review process that anytime that there is a adverse event we do a full medical case review with a group of boarded

specialists, and we go through all the different components or do follow-up laboratory work as needed to make certain that we know what is going on with that case. Next slide.

(Slide.)

So I will turn it over to Dr. Lewis.

DR. LEWIS: I'm Hugh Lewis, and I'm a veterinarian and in charge of new knowledge business called Data Savant. This slide is a simple one that just shows the acceptance over a period of a few years of moxidectin in our hospitals. At the time it was taken from the market, about 90 percent of the pets that we were seeing were being given the six-month treatment. Next.

(Slide.)

This is our incidence of adverse reactions using our internal system, and when we became aware of the concern that the FDA had about adverse effects we immediately reviewed our database. This is just some of the combinations of vaccines and other treatments just to put it into perspective, and you can see from just ProHeart 6 alone next to the end there we had 109 dogs that received only that and 4.4 cases per 10,000 adverse effects. The adverse effects are delineated on the bottom right-hand corner, and 0.8 per 10,000 of anaphylactic reactions. So this is very much within the range both qualitatively and quantitatively

that we see with vaccines, and for us this puts a great deal of perspective on the product and it seemed to be as safe as vaccines.

MS. SINDELAR: Thank you very much, gentlemen.

DR. : Last slide? There is one more.

DR. CRAIGMILL: I am afraid the time has expired, sir.

MS. SINDELAR: Thank you. Our next speaker is Lauren Simpson.

MS. SIMPSON: Hi. My name is Lauren Simpson. I have no financial gain with any organization or any group. I would like to thank everybody for allowing me to speak today. Let me clarify I am not any kind of scientist, vet, or in any medical field. But as a --- I have started collecting information regarding this drug, especially after my Pug had a reaction to ProHeart 6 back in April of '03. Very minor compared to what you guys see and hear about today. She was only getting this injection because the vet was conveniently out of her normal preventative. Later I found out it was suggested that vets carry only one preventative so as not to confuse the consumer with choices.

I stand before you today, though, not just as an individual, but for thousands of caregivers that feel

their companion is part of their family and not just a dog. When they were told this product was safe, "There’s no reactions. It’s better than monthlies," they thought they were doing the right thing for their dog. Then to watch them suffer and possibly die spending hundreds, thousands of dollars trying to save them, all the time being told by their professionals, "No, it cannot possibly be ProHeart 6 because that is safe," or being the reaction is too soon or too late, or that this type of reaction "Has never been reported to us before." The guilt we have all felt because we not only okay’d this drug, we paid for it and blamed ourselves for not researching it.

I recommended "Rainbow Bridge" more times than I could ever think possible, but I’ve been told recently we have a ProHeart 6 bridge now. But we are here to discuss the safety of ProHeart 6 with our pets. Safety seems to have been sidelined for our pets either for the almighty dollar or something bigger. There are two parts of ProHeart 6 to consider, moxidectin and also the delivery system. Microspheres are new in the vet world. They are also new in the human world where they are being used for females with uterine fibroids. They are described as little golf balls that emit moxidectin. They are supposedly fragile. Directions say shake to mix, but then once it has

been stored you only roll it gently. I can't help but wonder what happens to these microspheres after an injection if the dog is roughhousing or playing and that injection site gets hit. Remember, we are talking everyday dogs, not dogs kept in a cage.

Moxidectin is used in horses, cattle, sheep, and many other animals. It has been tested on fish, tortoises, humans. It's administered by gels, porons, orally, injections, and time-released injections. In 2000, ProHeart 12, also known as SR 12, was approved in Australia as a one-year preventative, just nine months before the approval here in the United States. Australia may not have the adverse reaction reporting system as we do here, but they do have one, although little known to the public, and they do have reports that have already been evaluated as probable and possibly related.

The manufacturer has stated repeatedly in the last three to four years that ProHeart 6 is not effective against adult worms, that it is not effective for microfilaria clearance, but that circulating microfilaria may decrease. Yet in 2000 the World Health Organization say the single treatment produces slow death of adult worms in dogs. Not effective for microfilaria clearance, but on page 30 of the document you have before you they admit

microfilaria counts were reduced to almost zero three weeks after treatment. I have no doubt that the manufacturer presented testing that was required by the FDA CVM at that time, yet I wonder was it ever taken into consideration that being innovative maybe more testing should have been done.

Alabama did testing for heartworm-positive dogs; 20 dogs were in the test, 10 were in control, 10 dogs received ProHeart 6, but only at three times the regular dose, and they were sacrificed only after 28 days. Texas did testing for repeated doses. The tests lasted three years according to FOI summary, but look deeper and apparently only four dogs received a regular dose of ProHeart 6 every six months for three years. Extensive testing.

In field trials, FOI summary in the document before you it states 200 dogs received regular doses of ProHeart 6 for a year and that three died. Then a press release to Chicago and Boston CVS in February of ‘03 they stated that 330 started this trial, receiving ProHeart 6, and only 280 finished. That is a difference of 50 dogs. In document they present to you on page 27 it states that in an 18-month study 12 dogs died or were euthanized, and apparently after the manufacturer’s review their deaths could not be attributed to ProHeart 6. I wonder what it was

attributed to? Old age? Heart failure? Liver failure? Kidney problems? Or maybe while crossing a street they had a seizure and were hit by a car.

We all know what the label states, so I won't repeat it here. Give to healthy dogs. Use with caution on sick dogs. How much caution can you use with a six-month time-released formula with no antidote except not to use it? According to charts I found suggested ages to start geriatric screening can be as early as four years of age for a larger breed. Were there any warnings for this?

MS. SINDELAR: Thank you, Lauren. But please remain standing because our next speaker, Ingrid Zorge, who registered --

MS. SIMPSON: Ingrid Zorge is not here today.

MS. SINDELAR: Correct, and she requested that Lauren Simpson please read her submission. Thank you.

MS. SIMPSON: She wrote it. She sent it to me. She wanted me to introduce you to Tigger and to Mac. Her name is Ingrid Zorge and she is a legally blind Canadian citizen, and she would like to offer apologies for not being personally present to give her statement. But the priority had to be taken care of, her dying dog which passed away yesterday.

"I would like to state that all the

information in this statement are my personal opinions only and conversations I recall to the best of my knowledge. On May 27th, 2004, I made a decision that would forever change my life. I agree to allow my vet to give a ProHeart 6 injection to all three of my dogs. One of those dogs was my lifeline, my seeing eye dog named Tigger, a 10-year-old Golden Retriever. I had raised Tigger from a sickly six-week-old puppy into a happy, healthy, and extremely intelligent friend who later was privately trained to become my sight. During the course of his duties as a service dog Tigger saved my life twice in traffic. I cannot begin to explain the bond that we shared or the depth of my feelings for this extraordinary animal who is my best friend.

"Within a few hours of receiving ProHeart 6 Tigger developed diarrhea, vomiting. He became lethargic, depressed, weak, lost his appetite. At times he would collapse on the floor too weak to stand. These symptoms continued, and after three weeks of supportive vet care an ultrasound revealed tumors on his spleen. His spleen was removed and during the surgery it was discovered that he had many more on his liver and his abdominal cavity was full of blood. Tigger did not improve from the surgery, and after about a week he died a painful, horrible death, vomiting blood, suffering through his back legs.

"He diagnosis was hemangiosarcoma, a canine cancer. This cancer did not develop nor did it end by normal standards. He was healthy, happy, and energetic prior to this injection. This cancer is usually diagnosed by ultrasound only after the dog has shown signs of weakness and collapse. Several studies suggest the average time until diagnosis is eight weeks. Usually the spleen is removed, the dog makes a positive recovery, and the average life expectancy is three months.

"My second dog to receive ProHeart 6 on the same day was Mac, my seven-year-old Rotty. Mac also vomited several hours after receiving the shot, but he appeared to return to normal in a day or two. In July and August, about six to eight weeks after the shot, Mac began vomiting, lethargic, had a fever. His symptoms increased. In November, '04, he had an ultrasound which showed tumors on his spleen and liver. Diagnosis, same as Tigger. Again, Mac was happy, healthy, very energetic prior to receiving the ProHeart 6 shot. Yesterday, January 30, Mac collapsed again and began vomiting. I was forced to make the painful decision to have him put down by our vet. This beautiful, courageous animal fought for his life to the very last minutes, struggling to rise even though he was heavily sedated. I will carry this disturbing image for a long

time.

"Three days ago, January 28th, my third dog who had received ProHeart6 on the same day collapsed, vomited, many pools of blood and bloody diarrhea. Rain is a one-year-old Border Collie mix and has had intermittent vomiting and diarrhea for the past six months. We are waiting for the test results now.

"There are approximately 1,000 diseases that can affect dogs. The mathematical probability of all three dogs developing the same cancer within this time period would be about one in 160 million. Think about it. Three breeds of dogs, three different ages, three different diets, only one common denominator. Do I believe that ProHeart 6 is safe for my dogs? Absolutely not.

"Drug companies are powerful entities. I am sure we would all agree to that, but with power comes responsibility and accountability. Fort Dodge, a division of Wyeth, manufactures ProHeart 6 in the United States. These vials of ProHeart 6 are then shipped to Canada and distributed to Canada vets by Wyeth Animal Hospital. In the US there have been recalls for ProHeart 6 due to varying factors. I believe this recall was to be international in May, yet there was no actual recall done in Canada. In the United States there have been three label revisions, new

package insert, Dear Doctor letters issued to US vets due to reported adverse drug reactions. Why was this information withheld from Canadian vets and consumers? Why did Fort Dodge, the sole manufacturer of ProHeart 6, only make three label revisions for vials of ProHeart 6 sold in the US? Why did Fort Dodge not send Dear Doctor letters warning of adverse reactions to ProHeart 6? Why would representatives of Wyeth Animal Health here in Canada not feel responsibility to inform Canadian vets and consumers of reported adverse reactions including deaths?

"My vet or myself would never have allowed my seeing-eye dog nor my companion dogs to receive this had we been informed of the possible dangers. Two different executives here in Canada have told me that they are not required to distribute this important information to Canadian vets or consumers. Why not? Are we as Canadian consumers not entitled to make informed decisions? Obviously not. In Canada our veterinary drugs are approved and regulated by the VDD similar to the CVM in the United States. The VDD is a division of the Health Canada system. I have questioned the VDD several times --."

MS. SINDELAR: Thank you very much.

MS. SIMPSON: Okay. Thank you.

MS. SINDELAR: Our next speaker is Laurie

Rentas.

MS. RENTAS: My name is Laurie Rentas. I have no financial relationship here with anyone, and in fact the only financial relationship I have had was with the vets that I paid to have my dog die anyway. I am here today because on February 5th of '04 ProHeart 6 destroyed a member of our family, our Yorkie Murphy, after a nine-month agonizing and ultimately losing battle. My initial intention was to focus my time on her loss, but based on the other tragic stories that came to my attention and showed me that the impact of ProHeart was much worse and much bigger than Murphy's case, I chose to address that.

We didn't want her sacrificed so that other dogs could be saved. We didn't want our lives changed forever, and we most certainly didn't want to end up a statistic of an unsafe drug and a pharmaceutical company that seemed to be ambivalent however we are. And because we are, I want this panel to know even more the horror stories regarding

ProHeart 6. I want to say right now that at no time have I ever or will I ever claim to be a scientist, a statistician, or an expert regarding the knowledge I have of ProHeart 6.

The totally voluntary and unsolicited data I am about to share with you came from a website called CAPS.

The president of CAPS created and made available a ProHeart 6 complaint form because she knew of people who suffered at the hands of ProHeart and wanted to see who else was out there and going through the same thing. Complaints rolled in on almost a daily basis. Keep in mind that at no time did anyone go out looking for these people. They found CAPS because they were looking for answers, but they found as did we that there was no going back once this poison was put in your dog's body.

There are far more deaths than anyone was lead to believe, all which came as a result of a product that was supposed to offer safety against heartworm, and the veterinarians lead us guardians literally to slaughter by misleading us as to the safety of ProHeart as the new, convenient alternative to the monthly drug. But in reality, it was an unsafe heartworm prevention promoted over the perfectly effective products that had been on the market for years. We went to these veterinarians because we trusted them to know more than we did regarding heartworm prevention, and we accepted their recommendations.

There seems to be a denial factor here in these vets. Out of all these reports that came in through this CAPS website, only 10 positive comments were made by the guardians that their vet even tried to help them or was

at least empathetic and open to the possibility that ProHeart could be causing the problem. Most vets wouldn't even engage in conversation regarding the possibility. Guardians basically hit brick walls trying to fix what was happening to their pets, and the brick walls were Fort Dodge and the vets that we trusted in the first place.

I won't even address the thousands of dollars we have thrown away as a direct result of ProHeart. There was a test for every symptom, and all it took was a credit card from the guardian to carry it out. Yet definitive answers as to those problems were never forthcoming.

So were the vets lied to? Who lied to them and convinced them of the effectiveness and safety of this product? All of us in this room were informed that the purpose of the hearing is to determine the safety of ProHeart 6. ProHeart 6 is not safe. The comparisons against all of the monthly tablets prove that. The numbers show unequivocally that there are not the same degree of adverse reactions in the monthly prevention drugs.

Unfortunately there are still people out there who are in the midst of fighting what Proheart 6 is doing to their dog since it has only been five months that it has been off of the market. So we know that there are still dogs with this in their system. There was never the

degree of effort stopping the use of ProHeart that there was in couching us all to use it. In fact, there are reports of dogs receiving this after the recall.

Of over 60 adverse reactions, they came from over 35 states. There was no rhyme or reason to the drug's effect on size, sex, or age. There's practically equal numbers of both male and female. There are dogs from age 15 down to puppies six-months old. Seven-years old was the most common age reported for death in what we collected, with four-years old being second. We have complaints from Chihuahuas and Yorkies to Great Danes and to St. Bernards. 70 of the 174 guardians, which translates to over 40 percent, responded that on that day the only thing administered to their dog was ProHeart 6, 40 percent. But the most disturbing fact to come of all these statistics is this: Out of the 174 voluntary reports, 80 of these dogs have died so far. Think about it, 46 percent.

If Fort Dodge truly feels their product is so safe then I question why a company of your magnitude would offer thousands and thousands of dollars in hush money if you have nothing at all to hide. One and only one common denominator among all of this data? Right, ProHeart 6.

MS. SINDELAR: Thank you. Our next speaker, Janice Storey.

MS. STOREY: My name is Janice Storey, and my dog died in October of 2002. Two-and-a-half years I've been waiting for this product to be recalled. Many thousands of dogs have been affected. I have in my possession two other dog owners have asked me to cite the conclusions that veterinary specialists after determining, after thorough examinations and extensive testing, how ProHeart affected their dogs, and the case numbers have been presented to the FDA and Wyeth. One of them is in California, an attorney, and that case number is 80840-05. The other one is a -- the name of the dog is Pickles. The other one is case number 200402016, Rusty, a six-year-old champion Doberman in Dallas.

Also my dog, four vets, not one, not a single on vet would ever admit -- the product had only been on the market one year -- that my dog could possibly have been harmed -- actually I was told could never be possibly harmed by ProHeart 6. However, my new personal vet, I submitted his x-rays which had a huge amount of spots on them, to him. He submitted it to an utmost heartworm specialist. I can't say names here, but he appears on the Wyeth front page of your website, so you would know who that would be, and he is at Auburn University. So you all can all figure it out. He looked at my x-rays and he said that it is difficult for

vets sometimes to look at these x-rays and determine if it is in fact heartworms or if in fact it is cancer. So he looked at my x-rays and he determined as told to my personal vet that it was pulmonary thromboembolisms. Furthermore, my own dog's testing, the very first vet that I took him to, he had written down PTE remarkable. I had no idea what PTE is. I later found out it means pulmonary thromboembolisms.

My dog had hidden heartworms, and he had tested 11 years due to being on Heartguard Plus. Any monthly preventative out there is capable of making the female worm sterile with prolonged use. The testing is inaccurate on low female worm burdens. Therefore any dog that receives a ProHeart 6 is at risk. I have documentation whereby the dog in Dallas, it cleared the adult heartworms in 33 days and the microfilaria in 45. Has Wyeth ever contacted this specialist? No. Furthermore, the personal vet of that same dog, Rusty, heard from Wyeth one time. They have yet to have ever been paid, and that was a year-and-a-half ago. But Wyeth will pay the vets that don't speak out against ProHeart, and that is the problem the public has. We can't convince our vets if they are brainwashed by Wyeth. They are afraid of Wyeth. They buy products from Wyeth. It is very difficult for us to prove to you. Furthermore, any of you vets here know that in the

clearance of microfilaria that it can create IMHA. You also know -- I have a study here from Japan, a clinical research data, a published veterinary journal. It shows what happened to microfilaria-positive dogs.

So, yes, I'm emotional about this. I'm mad about this. I am not going to read to you everything. You can read it. You have the case numbers. You can read what the vets concluded. I'm tired of the vets that promote the product like Banfield who is going to acquire a lot of money because we come in every six months and spend our money. This product -- and I'm mad at the FDA. They should have never approved this product. There was not enough research done. Only 200 dogs in Australia for microspheres, but that was extensive testing. It was in two veterinary clinics and students were overseeing it. Why don't you all investigate the microspheres?

Why don't you investigate what's really going on here? They are obtaining research on our dogs, and they are using it to further their vaccines in my opinion, and that testing can be tied to the fact that in October of '03 they had a first injection for humans that they announced. Okay? And in March of '04 they announced their affiliation with TR and World Health Organization. So this isn't about just a heartworm shot. You vets have been mislead. You are

being used as a tool to inject the dogs, and they pay for the tests and they win. We lose. Our dogs die. We can spend thousands of dollars to protect them. So I'm angry. I'm sorry, but I am angry.

MS. SINDELAR: Thank you for your comments.

MS. STOREY: So -- thanks.

MS. SINDELAR: Our next speaker is Jean Brudd.

MS. BRUDD: Good afternoon, Ladies and gentlemen. Let me first state that I do not have a financial interest or relationship with any group or company or whatever. I paid all my travel expenses to get here. I jut want to say that I am here today on behalf of my two diseased dogs, Tasha and Nicki. They died during the peak period of 2002 due to one shot of ProHeart 6. My survivor dog, Casey, is on the low end of normal. Again, two-and-a-half years later, and his immune system was compromised.

However, I am not speaking here today on behalf of my dogs. It's still too painful for me to talk about two-and-a-half years later. Slow down here. I just want to say that most of the people speaking this hour are not a bunch of fanatics on the internet as we have sometimes been called. We are here because we have been victims of ProHeart 6. Our dogs took ill. Many of them like my dog

died. Some may say that these are just dogs that can be easily replaced, but not for us. These dogs were and are our family members. For some of us our dogs are the children we never had and never will have.

I am sure each of you in this room has bonded with a child. Perhaps it is one of your own. Your love for this child is so great you cannot imagine your life without him. Imagine a drug you agree to be given to this child to keep him in good heath. Imagine this child adversely reacting to this drug and there is no known antidote to counteract its adverse effects. Imagine this child having to suffer through the adverse effects for many months until the drug passes from his body, if his body can live that long. Imagine the horror of watching day after day your child seizing on the floor, or walking into walls, or not being able to eat or drink, or urinating or defecating on himself, or blood coming out of every orifice of his body, he is crying out in pain, and there you sit powerless not able to do a thing to help him. All you can do is turn over your child to the doctors, the so-called experts, and hope the doctors can figure out how to treat him, because they sure as heck don’t know what is wrong with him, and it sure as heck cannot be the drug that they administered to your child.

Your doctor won't admit it if he thinks it is the drug because he doesn't want to be slapped with a lawsuit, and the manufacturer won't admit it because they don't want to be slapped with lawsuits. Meanwhile, you sit in desperation and pray that God fixes it all, brings you the miracle you are so desperately praying for, but the miracle never comes. You are faced with quality of life issues for your child who is never going to eat or drink on his own, walk, talk, play again. So what do you do? Do you let him suffer, or do you play God and pull the plug? Either way your child dies, and all you can do is blame yourself because it was you who trusted your doctor when he said this product was safe. But you played a part in killing your own child. How do you live with yourself for the rest of your life?

Welcome to our world. This is our own private living hell, the world of thousands of us guardians who have our dogs, our family members, adversely effected and even killed by ProHeart 6. If this happened to your child would you sit idly by? We think not. This product is not safe. You know it and we know it. The manufacturer will say that less than one percent of dogs are affected, that it benefits more dogs than it hurts. But when all the dogs in your household are affected by their product that is

100 percent, and it was 100 percent in my household.

Fort Dodge, we want you to stop experimenting on our children. Stop the killing. Stop this poison for profit. Members of the Committee, please tell them to leave our family alone. Look into your hearts and do the right thing by us and by our innocent, loving, animal companions. Please, do the right thing. Thank you.

MS. SINDELAR: Thank you four your comments. The next speaker is Dr. Martindale.

DR. MARTINDALE: Thank you. Other than purchasing Fort Dodge products I have no financial connection with the company. I am a practitioner in Denison, Texas. I own and operate a clinic for the past 36 years. It's a companion animal practice, and we did start using ProHeart 6 when it came out in 2001 and have progressively moved towards this drug as our primary heartworm prevention. Since the beginning we have experienced better compliance from our clients. It does fit well into our wellness program where we see the pet twice a year. It is readily accepted by the client, and we've had a marked decrease in the heartworm incidents over the past two years, ranging between 45 and 55 percent, depending on the year. Compliance was increased by sometimes as much as 60 percent in the two years that we have used it. So in our

experience it's been a very effective heartworm prevention without any serious side effects or any disease entity that we could directly attribute to its use.

We did have one small dog within 45 days after ProHeart 6 and vaccinations with immune hemolytic anemia. Interesting enough, though, that was the only case that we saw during the year. Whereas in previous years we historically would se anywhere from three to five cases of this disease.

Also I have had the opportunity to visit with many colleagues. My local colleagues, colleagues in Oklahoma, Texas, and Louisiana over the past few months before and after withdrawal. Every veterinarian that I've talked to said they have not experienced bad side effects with the use of the drug, and these veterinarians were giving anywhere from less than 500 doses to one veterinarian that had given 10,000 doses in Louisiana. So my experience has been good. I think if this drug is handled, stored, and administered correctly that it is a very effective means of preventing heartworm disease. Thank you.

MS. SINDELAR: Thank you very much. Our next speaker is Dr. John Gay.

DR. GAY: Good afternoon. Dr. John Gay, a faculty member at Washington State University. I am

veterinarian and have a PhD in epidemiology. I am the epidemiology representative on the American Veterinary Medical Association's Counsel on Biologic and Therapeutic Agents. My comments have been reviewed by fellow council members, and the Clinical Practitioners Advisory Committee. The AVMA paid for my travel. I have no financial interest in Fort Dodge Animal Health, and I am not engaged in clinical practice.

The AVMA is a national association recognized as the primary voice of the veterinary profession. We have some 70,000 members, which is 86 percent of all veterinarians. The AVMA's mission is to advance the art and science of veterinary medicine in all aspects, from clinical practice to food safety, to regulatory medicine to wildlife. We commend the FDA for holding this meeting and thank you for the opportunity to participate.

First, we believe a strong, science-based, transparent, systematic, post-market surveillance system is critical to our patients, to our clients, and to our profession. It provides important information that our profession needs to maximize the benefits and to minimize the risks for patients under our care. Our patients, ranging from finches to elephants, and Pekingese to Great Danes, present with a wide range of individual

characteristics and live in a wide range of environment. Because of this diversity we recognize that clinical trials required for new drug approval cannot be expected to detect all combination of circumstances and may lead to adverse drug experiences. We also recognize we cannot avoid all risk, that virtually all drugs and biologics have inherent risk as a consequence of their effectiveness. We recognize that to minimize this risk we must continually strive to improve our understanding of these and the conditions under which they occur.

A strong system reduces two general types of errors. First, it has sufficient sensitivity to provide early, clear detection of associations between particular drugs and adverse effects in particular segments of our patient population. In the long run, this is required to maintain the profession's confidence in the drugs we use and our clients' confidence in us. Second, it has sufficient specificity to reduce problems with spurious false association between particular drugs and adverse events in animals' lives. Again, this is required to maintain the profession's confidence in and access to these drugs.

Critical to a strong surveillance system and thus to reducing these errors is sufficient information. Increasing computerization of patient records and internet

access may provide several opportunities to increase reporting. One opportunity may be as simply as including URLs for direct adverse event reporting on every FDA approved drug insert. Another may be developing procedures to upload event information being routinely captured in electronic patient records, particularly in large corporate systems. This is already happening with HMOs and other care organizations in human medicine. Third, because the USDA is launching a surveillance system for adverse vaccine reactions, sharing of data between the USDA and FDA would improve the depth of comparative risk information for both agencies. As drugs, biologics, and pesticides are often used in combination, interagency collaboration including the EPA would enhance the detection of adverse effects resulting from particular combinations. Fourth, enhancements in the timely feedback of clinically relevant information to practitioners would help communicate the importance of reporting. Finally, it may be necessary for professional organizations to further inform the members on the critical importance of reporting adverse drug experience information.

To be as strongly science-based as possible, a pharmacovigilance system should incorporate all of the steps for logically assessing the strength of evidence for causality. The first step is using statistical analysis to

objectively determine the likelihood that any observed associations are due to chance rather than due to cause. Unfortunately, subjective assessment of count data for trends and clusters is fraught with danger. Statistical procedures to determine how likely apparent trends in counts or clustering events are due to random chance are well established. Quantifying risk is an important component of this process. However, reliably establishing and comparing risk requires sound exposure data, which is not routinely captured in the current system.

Finally, to retain trust and to maximize cooperation, the system must be sufficiently transparent to all stakeholders. Obviously the identity of individual patients and clients must be strictly protected. That marketing data providing for proprietary advantage must remain confidential. But if any party loses trust or reduces cooperation, animal health and ultimately the profession suffers. Again, I commend the FDA for holding this meeting, and I thank you for the opportunity to participate and to comment.

MS. SINDELAR: Thank you for your comments. Our next speaker is Connie Dominy.

MS. DOMINY: Good afternoon. My name is Connie. I am from Georgia. I went through snow, sleet, and

pure hell to get here, and the mic just came off the thing, but that's fine. I can improvise in five-minute period of time. Let me say first that I am here of my own accord. I do not represent any group, not have I received any monies from any group here. I paid my own way. I am here to represent --

MS. SINDELAR: --- slide presentation?

MS. DOMINY: Pardon?

MS. SINDELAR: Do you have a slide presentation?

MS. DOMINY: No, ma'am. I don't, and this is not at my five minutes, okay?

(Laughter.)

MS. SINDELAR: We will give you your time for it.

MS. DOMINY: Okay. That's fine. I'm sorry. Would you please restart the clock?

MS. SINDELAR: We will give you credit.

MS. DOMINY: Thank you. You know who I am, you know why I'm here, and you know that I do not gain financially from any of this whatsoever. I don't even own stock in pharmaceutical companies because I don't trust them today, even though they are a big business and I'm sure I would have monetary gains if I did.

By profession I am a psychotherapist and I have been in this field in private practice for over 20 years. I have been able to be familiar with product development and marketing statistics -- or tactics, I'm sorry, and post-approval safety data collection. My goal today is to challenge the FDA and the Advisory Committee to simply do your job. You are consumer advocates. The consumers are the animals, and they can't speak for themselves. You are charged to do this to the best of your ability and to not let politics, power, or greed intimidate your decisions. You are to hold the manufacturers of animal products accountable for their safety. I encourage you to look deeper than your soul and make the right decision regarding ProHeart 6.

I have a comment about Banfield that I have heard today. Let me just tell me that I went into our Banfield in Macon, Georgia six weeks after the product had been recalled voluntarily. They still had the advertisements up. That is not accountability. I'm sorry.

I remain firm in my belief that the symptoms my dog, Ready, who received the ProHeart 6 injection who is an Italian Greyhound and a champion, he received it and six months -- over the whole six months he exhibited symptoms, and I believe they were related to ProHeart 6. Fort Dodge

remains firm in its belief that their product is safe and science will prevail. Well, ladies and gentlemen, I am telling you here today that I believe that this product is not safe and science will prevail.

I have read the FDA report. I am appalled to think that Fort Dodge would interfere in the reports sent in by veterinarians as being -- referred to them as being over-reactive and biased. I believe veterinarians under-report adverse reactions. I believe that veterinarians are grossly mislead by Fort Dodge and their sales representatives. You ask about necropsy. By the time our animals get to that point we have spent major megabucks, and that is the last thing on our mind.

When looking at all of this with a scientific perspective, I question the validity of the initial studies presented to the FDA for product approval. To have a valid study the sample groups should represent the treatment time that this product is intended to work for. That at less than 180 days does not represent the study validity or reliability. The sample size was inadequate based on the projected population size and the dosages that Fort Dodge projected to sell, nor was it representative of a cross-section of the subjects that would receive this medication.

Another concern is the glaring absence of

longitudinal studies of significant sample size. It is interesting to note that the laboratory trial subjects were destroyed. This is otherwise known as destroying the evidence. In some areas this is a criminal activity. It is my opinion that Fort Dodge has been negligent in their job to provide a safe product. They have also failed in their job of apparently addressing the issues, the data collected post-approval indicated. They have categorically denied that the symptoms seen are not related to ProHeart 6. Denial of Fort Dodge is similar to that exhibited by the parent company when they denied what Phen-Fen was doing to our population, and we all know what happened with that.

So is this a systemic problem within this company? Maybe so. Is it a trend? Maybe so. It certainly brings me and I hope the FDA and the Advisory Committee to question Fort Dodge's integrity and their ability to provide unbiased information to the FDA and consumers. After all, the bottom line is profit, not safety or concern for our family members. This creates the biggest bias reported here today, profits.

As late as October, 2004, Fort Dodge was still denying that my dog's adverse reactions were due to ProHeart 6. I talked to the Fort Dodge Representative. They told me that they had contacted my vet and they had

been told that his case had been closed because he exhibited no other symptoms. Well, my little dog for seven months exhibited symptoms. They didn't contact. They didn't talk to my vet. I talked to the vet. The vet told me the same thing. Would you believe that? That vomiting and diarrhea are not side effects of ProHeart 6. It's on your brochure. I had tests done by ---. I had upper GI done. I had all kinds of stuff done to try to rule out ProHeart 6 at my own expense, ladies and gentlemen. Never did you contact. But yet you continue to deny, saying that because his symptoms, his primary symptoms, occurred on the 11th day -- I've heard seven to 14 days, ladies and gentlemen. I have a copy of his documentation with me. I encourage you to insist that more comprehensive studies be done on existing data and surviving subjects. Ready is alive. Let him be your champion.

One final parting thought. Until one has loved an animal a part of one's soul remains unawakened.

MS. SINDELAR: Thank you very much for your comments. Our next speaker is Georgene Paulauski.

MS. PAULAUSKI: My name is Georgene Paulauski. I'm a clinical specialist at St. Anthony Medical Center. I'm a clinical educator for Indiana University, and I --- college. I have no financial gain. I filed an

adverse reaction report in December of 2003 after Cletius received a ProHeart 6 injection. I was contacted by CBS-2 News in regards to what happened to my dog. The segment aired. Fort Dodge gave their account of what happened and published this both on the internet and through mailings to your peer vets throughout the United States.

I would like to read to you an excerpt of what Fort Dodge printed about my dog. "Initial testing identifies some abnormalities. Hemolytic anemia was a possible diagnosis. He was placed on antibiotics and corticosteroids. The dog's steroid dose was decreased. Shortly thereafter he presented not acting right again. After increasing the dosage, the dog's condition improved."

Now I would like to show you and let you see in reality during the seven months. These are the real facts, not what was published. Cletius received ProHeart 6 on September 27, 2003. No other injection. Immediately he developed a hot spot. Within weeks anorexia and became lethargic.

(Slide.)

Looking at the first slide I have up, in Fort Dodge's word there were some abnormalities noted. Anybody that knows a basic CBC, these are not some abnormalities. There are grotesque. These are panic value levels. This is

the case of Cletius and hemolytic anemia. He is in your packets. That's his number.

(Slide.)

Medical visits, we went through 45 office visits, two separate visits in ICU stays at Purdue University, multiple emergency visits, surgery.

(Slide.)

He had 102 lab draws, multiple types and cross-matches, multiple cultures including blood, urine, gastric, blood gas analysis, and ABGs.

(Slide.)

He had two ultrasounds, abdominal scans, numerous x-rays.

(Slide.)

This next page is hideous. These are the drugs it took to keep my dog alive during his hemolytic anemia. I am not going to go through the numbers. You can look at them and gasp.

(Slide.)

The fluids to keep him alive. Multiple keep opens, 0.9 normal saline, lactated Ringers, Hespan, blood transfusion, Oxyglobin, potassium chloride, Hetastarch.

(Slide.)

Due to all this multiple complications

resulted. You can't imagine anything worse on a hemolytic anemia than a dog starting to hemorrhage. That is exactly what took place. The dog started hemorrhaging, vomiting blood, tarry stools. At this time he also had grossly elevated liver enzymes. My dog's appearance became grotesque. Pot belly, enlarged liver, muscle wasting, the inability to walk, foot flop, swayed spine.

(Slide.)

Numerous attempts were made to try to wean Cletius from his immunosuppressants while the ProHeart 6 was in his system. Every attempt failed, and a lot of those attempts resulting in having to increase doses of Pred.

(Slide.)

Eventually he became over-suppressed and leukopenic. I then had to deal with bladder, bowel, and gastric infections, cystocentesis, diarrhea, numerous antifungals, antibiotics, LONOX were added. Little did we realize his over-suppression would finally become a turning point.

(Slide.)

After a lengthy conversation with Purdue and our vet, the debated on whether to decrease the dose of the immunosuppressant or finally withdraw it. The comment was made, "If it is truly the ProHeart 6, we should be able to

remove all meds and this dog should do perfectly fine."

(Slide.)

After him living on over 100-and-some medications weekly, on 6/2/2004 all meds were DC'd. I spent the entire summer rehabbing Cletius, walking, swimming, rebuilding his muscles.

(Slide.)

He is since now symptom free and drug free for 209 days. He has gone back to Interceptor without any incident. I am one of the fortunate ones here today He is healthy, happy, and extremely active.

(Slide.)

As a point of interest, my dog did have mild skin allergies. This was not his first injection. If you go back and look at your data, along with the ProHeart 6 when I went to the vet he said, "Is your dog itching?" If he was they gave him a shot of Depo-Medrol. Did that save him from a previous reaction? Absolutely. The steroid protected him.

(Slide.)

The long-term effects of all the meds to keep Cletius alive are yet to be seen, but what my family and this dog went through were pure hell. It consumed seven-and-a-half months of our lives. I can't begin to tell you

the bills, the time lost from work, without a single dollar recovered.

(Slide.)

It is very disheartening to know after seeing the clinical trial data after the fact I would have never have injected my dog with this knowing what you have published as an adverse reaction. Can I just give a closing comment? I say to Fort Dodge stop making excuses. You printed fluff about my dog, not faxes. As for the paper, shame on you. The hell that my family went through and what my dog went through? You continue to create a facade. You put it out on your internet, published it --

MS. SINDELAR: Thank you very much.

MS. DOMINY: Thank you.

MS. SINDELAR: Our next speaker is Paul Marron.

DR. MARRON: I do not have any financial affiliation with Fort Dodge. I'm not a government employee. I have paid my own expenses to come to this meeting. Members of the Food and Drug Administration, members of the press, fellow veterinarians, fellow companion animal providers, pet owners, thank you for this opportunity to speak before you.

As was mentioned, my name is Paul Marron. I

am a veterinarian and a practice owner at Battlefield Animal Hospital in Manassas, Virginia. I graduated from Texas A&M University in 1985. I've been in practice for 20 years, four-and-a-half years with the Army Veterinary Corps and 16 years in private practice. We currently have five veterinarians in practice at Battlefield Animal Hospital. We provide veterinary care to almost 7,000 companion animals.

The veterinarians at Battlefield Animal Hospital have as their first and foremost concern providing safe and effective products to insure the health and well-being of our clients' pets. As such, we were excited when a product became available that would not only improve compliance for parasite prevention, but also significantly reduce parasite disease and exposure to pets and pet owners. In July, 2001, we began providing ProHeart injections to our clients. Since then we have given 2,357 injections with only two verifiable minor reactions to those injections. During this period we have not seen any evidence of any increase in disease conditions in the pets treated at our hospital. For our experience it speaks for itself. ProHeart in our hands has shown itself to be a safe product.

Before the introduction of ProHeart, our clients were faced with only one choice in heartworm and

intestinal parasite control. That was oral medication. Though oral medication is effective, compliance has always been a major issue. At our hospital, we remind our clients by phone, by regular mail, by email, and during hospital visits to be sure to give the oral medication to their pets. Even with our efforts and the good intentions of our clients, compliance among our clients was at best 30 percent. Only one out of three of our clients' dogs were consistently protected. That means a higher exposure potential for internal parasites for our clients and their children.

As you know, transfer of parasites from our pets to us and our children has become a very real concern, not only for the veterinary profession, but to those of you in the regulatory professions. The Center for Disease Control in a recent survey of animal shelters revealed that almost 36 percent of dogs nationwide and 52 percent of dogs from southern states harbor intestinal parasites. At least 3,000 to 4,000 serum specimens from human patients are submitted to the CDC, state public health labs, or private labs for sero-diagnostic confirmation of intestinal parasite disease. The CDC further recommends that practicing veterinarians can provide an important public service by recommending fecal examinations twice yearly and providing

well-timed --- treatments. The Companion Animal Parasite Control Council recommends that fecal exams on companion animals be conducted two to four times per year.

Ladies and gentlemen, the reason I provide these statistics is to inform you that the use of ProHeart at our hospital has been one of the most effective means in helping to follow the guidelines for preventing internal parasitism in our pets and transmission to our clients and their children. In our practice and with the use of ProHeart 6 injections done every six months, fecal exams are now availably done twice yearly. In addition, it has helped to greatly improve compliance for internal parasite exams and treatments. As a result of utilizing ProHeart 6, our compliance for intestinal parasite exams, heartworm tests and prevention has increased from 30 percent to over 80 percent. That, ladies and gentlemen, is a significant improvement in protection for our pets, our clients, and their children.

Members of the FDA, it is my opinion that the current risk assessment strategy being utilized is flawed. The unfiltered reporting system utilized to evaluate the safety and ultimate recall of ProHeart 6 has to create confusion with pet owners, veterinarians, and the public in general. On the one hand, we have thousands of

veterinarians nationwide who have provided tens of millions of doses of ProHeart with few complications. And on the other hand, we have claims of a potentially deadly drug. On the one side, I speak to my clients about the safety and efficacy of a safe, convenient, and effective drug. On the other side, they hear media reports and internet hype, opinion, and conjecture of serious complications.

I encourage a revision of the current reporting system to insure that review of drug safety is done by factually, scientific, examined discourse and weight of evidence. Not with conclusions and actions being taken as a result of the seriousness of the charges. It greatly concerns me as a veterinarian that I have been told that there are those in regulatory agencies who believe that, quote, "Veterinarians cannot be trusted to report accurately the adverse reactions to ProHeart because they are simply trying to protect their own interests and are seriously under-reporting the adverse reactions associated with ProHeart." Unquote.

I hope that these reports are not true. First, this type of self-promoting talk is grossly inaccurate and unprofessional. It is does not encourage cooperation and communication. Second, it seeks to promote an attitude of distrust between veterinarians and their

clients. Finally, I would like to restate that the veterinarians I personally know have as their first and foremost concern for the providing of safe and effective products for our clients and their pets. The goal of our profession is to improve the quality of lives of our pets and improve the client-pet bond while at the same time reducing the risk of disease being transmitted from pets to owners and their children. As a member of one of the greatest professions I again thank you for this opportunity to address this Council.

MS. SINDELAR: Thank you for your comments. Our next speaker is Dr. Bob Rogers.

DR. ROGERS: I'm Bob Rogers. I am a private practitioner in Houston, Texas. I have no conflict of interest, financial or otherwise. I want to applaud the FDA for the action they have taken to product the public by the withdrawal of ProHeart 6. The adverse reactions that I witnessed in my practice fall into three categories; neuro-toxicity manifesting in the form of seizures, pulmonary symptoms including massive pulmonary thromboembolisms resulting in death, allergic reactions including hemorrhagic gastroenteritis progressing to disseminated intravascular coagulation and death.

The following questions need to be answered

before this drug is returned to the market. Are these problems due to an inherent problem with the drug moxidectin, instability of the microspheres, allergy to the microsphere coating, or are they due to mishandling of the drug by veterinarians or perhaps some of both?

If ProHeart 6 is injected through too small of a gauge needle or if the bottle is reconstituted and then shaken vigorously after several nights of refrigeration instead of swirled, could this cause disruption of the microspheres? Could disruption of microspheres cause premature release of the moxidectin, moxidectin overdose, and resulting seizures? Or could this be an intermittent manufacturing problem?

We know moxidectin is a more potent filaracide than ivermectin or milbemycin. In a letter I have from another veterinarian dated February, 2002, she says that her patient died from a pulmonary thromboembolism as an adverse reaction to ProHeart 6. She states that Dr. La Roch at Fort Dodge told her they knew ProHeart 6 could kill L4 and L5 larvae. Fort Dodge did not send out a Dear Doctor letter to warn veterinarians not to give heartworm to heartworm-infected dogs until November of that year, nine months later. Does the death of L4 and L5 newly-emerged, young adult larvae and possibly the death of migrating

intestinal worm larvae, all of which cannot be detected by available testing methods, post a fatal risk to our patients? How can this risk be avoided?

How does ProHeart 6 cause hemorrhagic gastroenteritis? Is this due to the death of migrating larvae, or is this a manifestation of allergic reaction?

What is the cause of mast cell degranulation? Are dogs allergic to the hydroxypropyl methylcellulose? Do these anaphylactic reactions result in DIC? Is there a hapten somewhere in this formula that we don't know about as was the case with diethycarbamizine? What is the cause of the auto-immune reactions?

If microspheres are injected into a dog, do some of them enter the circulation? What is the impact of circulating microspheres on the kidneys, liver, and lungs? Studies have shown in other species that microspheres can cause pulmonary hypertension.

Looking at the ADEs it seems a number of product failure reports and end effects increased with time. Is this due to laxity of testing on the part of veterinarians?

Finally I have a suggestion which could increase product safety. Unit dosing has been widely mandated for human drugs. If this product is returned to

the market, unit dosing would help to prevent many of the mishandling and storage errors.

I want to express dismay at the method in which this product was marketed. Please help me to understand why a company would choose a person whose presentations involve so much profanity? Dr. Whitford is not a board-certified cardiologist, not a parasitologist or pharmacologist. He has no qualifications. In his presentation he focused on one point. Veterinarians will go broke due to competition from Pet Med Express if they don't switch their clients to this product. He stated that allergic reactions could be treated with Benadryl. Since when is Benadryl the standard of care for DIC? He repeatedly said that all of the adverse drug experiences reported to the FDA are not due to ProHeart 6. For a company to deny all FDA ADEs is not responsible. He did nothing to emphasize the need to handle the drug carefully and the consequences of not following the label directions.

In my humble opinion, Fort Dodge is responsible for this mishandling of this drug by veterinarians and the death of pets that have resulted because they not only failed to warn veterinarians about the side effects, they denied them, and the failed to adequately inform veterinarians on the proper handling of their drug.

This lack of responsibility is no in the best interest of Fort Dodge, it is not in the best interest of our patients, and it is not in the best interest of the veterinary profession.

If this drug is returned to the market, the FDA needs to mandate that Fort Dodge implement a thorough training program to insure clients are warned and to insure that veterinarians are instructed on the safe use of the drug. FDA mandated programs have proven very effective increasing safety of drugs in past like Tilcomycin and Revolution.

Now Banfield has an excellent employee training program and --

MS. SINDELAR: Dr. Rogers?

DR. ROGERS: Yes.

MS. SINDELAR: Thank you very much.

DR. ROGERS: Than you. Our next speaker is Stephanie Shain.

MS. SHAIN: Thank you. I'm Stephanie Shain. I'm here from the Humane Society of the United States, and on behalf of our over 8.5 million members and constituents, the majority of whom are pet owners I am here today. As a matter of course, the Humane Society does not offer our opinion on veterinary drugs. We choose rather to leave that

to the individual veterinarian and client relationship. We make an exception for ProHeart 6 for two reasons. Number one, the enormous number of animals that were adversely affected by this drug; and, number two, the fact that it is a preventative drug and not something to treat disease.

I am lucky as an individual pet owner of four very healthy dogs that we chose not to use ProHeart 6 when it was offered to us by our veterinarian, thinking rather our monthly works, we know it's safe, and a six-month injectable just seems too good to be true. We ask because this is a preventative and because there are many known safe other drugs that can prevent heartworm safely that this drug not be released back onto the market. We think to do so is just simply reckless and too great a risk for individual pets and their owners who will invariably suffer from it. Thank you.

MS. SINDELAR: Thank you for your comments. Our next speaker is Kerry Tuttle.

DR. TUTTLE: My name is Kerry Tuttle. I'm a veterinarian from Peoria, Illinois. I have been in practice for over 30 years and am the director of three hospitals in Peoria and Bloomington, Illinois. We have approximately nine veterinarians working for us, most of whom have been with us for over three years. In late 2002, being somewhat

of a cynic with all new drugs that come on the market because of problems that have later been found once they have been presented, we did not begin ProHeart 6 upon its initiation. Late 2002 we gave our first dose, and since that time we have given approximately 6,000 doses. It represents just over half of the heartworm prevention of the clients that we have in our practice.

We offered our clients the choice of the once-monthly heartworm medications and the ProHeart 6. In that time, since we began that, which is over two years until the time it was removed from the market, via three-day callbacks, the fact that we have three practices that are relatively small practices, three doctors per practice, we feel that we know our clientele reasonably well and our clientele knows us. If they have a problem they tell us. If we think that they have got a problem, we morally accept some responsibility to solve that issue, I think no different than most veterinarians.

In the two years that we have given ProHeart 6, the 6,000 doses, we have documented four adverse reactions. Of those two were transitory digestive upsets, one was facial swelling, and one was hair loss at an injection site. The only one that has maintained or has been a continued problem has been the hair loss at an

injection site. It didn't grow back and probably is the size of a half dollar at this point.

Our efficacy as far as the drug has been essentially 100 percent. Compliance on the part of the clients has been good. We do give them the choice. We have advised them that there have been adverse reactions. To each doctor they have their preference to their client as to which they may provide voice inflection or at least provide which they recommend. As I said, we are over 60 percent or slightly over half with ProHeart 6. Art the time of the recall we had approximately 5,000 doses in stock. We questioned whether or not to send it back. Shortly we decided that immediately we would send it back because it was the right thing to do. Since that time all we have heard from clients is, "Don't you have an extra shot of that around somewhere, Doc? We want it. It's great."

I empathize with the individuals here today who have had disastrous reactions. We have not seen those, and I empathize with your group in the FDA because you are getting certainly some diametrically opposed information here, and I don't know you decide what's right and what's wrong. Thank you.

MS. SINDELAR: Thank you very much for your comments. We have exceeded the time allotted for the open

public hearing. I would like to yield the floor to Dr. Art Craigmill. Thank you.

## Committee Deliberations

### Dr. Arthur Craigmill

DR. CRAIGMILL: Thank you, Aleta. We will spend another half hour until we take a break. I think one-half hour. Is that your plan? Until 3:00, so it is 45 minutes. I would like to at this time to return to asking the committee if they have questions, and I think maybe in the interest of efficiency we will simply start going around the table, and I will skip people who have already talked and then come back for clarification. So I would like to start with Dr. Aref please.

DR. AREF: I sort of have spread out questions from various places. On page 18 in your -- the document from Fort Dodge, it says that about the carcinogenicity studies that the mice and rats that had the two-year study that doses were lowered because mortality was increased. Then the last sentence is that there were not compound-related findings in hematology values, organ weights, or at macroscopic or microscopic examination. There was no evidence moxidectin-related target organ toxicity or tumorigenicity.

So for a lay person what does that mean?

That you -- I mean, you obviously saw higher mortality, but you didn't see any symptoms or any changes in the various -- ?

DR. ROBB: I will ask Dr. Blasak to respond to the toxicology questions.

DR. BLASAK: Yes. Thank you. My name is Dr. William Blasak. I'm with Wyeth Research, and the carcinogenicity studies were done in mice and rats as they are typically done to assess carcinogenic potential because it is a disease that tends to happen more in later years of life. Those species have very relatively short life spans of one to two years. So there are commonly used for that.

The way doses are typically chosen for those types of studies, they are typically chosen on what is called a maximum tolerated dose. So you feed -- in these particular examples you feed the animals a certain amount of the test article, in this case moxidectin, and you maintain them on that diet. Now if that dose is too high generally what you will see is you will see some kind of toxic effects. Okay? And the effects that we saw were very typical of what is seen with moxidectin, and that is they stop eating, okay, they begin to lose weight, and if you go on long enough, okay, you have mortality in that study. Now obviously you cannot study the carcinogenicity in animals

that are no longer there. Okay? So the reason of reducing those doses is that we were too high in those doses. Okay? And so as the studies were going on -- I think it was within about the first month or so we noticed these decreasing body weights in these animals versus control animals. Okay? So we reduced the dose of moxidectin in the diet.

DR. AREF: Okay. So this was just a carcinogenic study so that you were only interested if they got cancer?

DR. BALSAK: No. No, and at the end of these studies -- so once those doses -- once the animals, if you will, stabilize at the lower dose, okay, the study has gone on, the animals are monitored on a daily basis. Okay? Then at the end of the study hematologies are performed, clinical chemistries are typically performed, and a full histopathological analysis of all the organs and tissues is conducted. Okay? And the main reason to do that obviously is to look for tumors first of all, but you also will find any kind of systemic organ or target organ toxicity in those animals. So if there were liver lesions resulting from moxidectin you should find them, if there were kidney lesions, et cetera.

And if I could add, it is not in the package, but we did a series of pharmacokinetic studies to supplement

what Fort Dodge had done. Okay? And the reason we did the pharmacokinetic studies is we wanted to know by the diet route how much moxidectin those rats were actually being exposed to, because we weren't sure. We weren't sure how much would be absorbed through the diet. Okay? And so we put those studies on in November actually to help address some of these issues, and if you look at what the rat consumed over the two-year period versus what a dog would be given over a two-year period with ProHeart, that is four injections, and you look at the actual exposure in the blood of those animals to moxidectin -- not just how much you gave them, but the actual levels in the blood -- those rats received about 860-fold the amount of moxidectin that dogs receive in a two-year dosing regimen. That is how exaggerated the moxidectin levels were in that study.

DR. AREF: So what did cause -- I mean, that they didn't want to eat and the weight loss?

DR. BLASAK: Well, you know, it's not uncommon in these effects. It is not uncommon when an animal is taking in too much of anything. Okay? There can be CNS effects. There can be effects on a variety of all biological phenomenon where they will stop eating, and we know that there is CNS effects of this drug. We know that from a variety of different sources, let alone just the

macrocyclic. But it is the exposure of the animal to the drug that is really in question. Okay? So if they were getting 860-fold the amount of drug over two years, if they were getting more than that maybe that did cause some effects, but, you know, the exposure differential there is so large that its relevance to a clinical practice is really in question.

DR. AREF: But would a necropsy show anything?

DR. BLASAK: No.

DR. AREF: So if you do a necropsy on dogs who have gotten ProHeart 6 you wouldn't see anything either?

DR. BLASAK: That's correct, and the dog studies for example, we have done a whole series of studies in dogs. He longest term study was a one-year study. Now this is a study were dogs were given again in the diet moxidectin for one year. So they got to eat their chow every day with a certain amount of moxidectin in it for over one year. Okay? And at the end in those dogs, and absolutely a good case, they did not lose weight. There were no adverse findings in life, and upon necropsy they went through a very full necropsy, a very systematic necropsy where all the tissues and organs were examined, and hematology, clinical chemistries, all those sorts of things

were looked at, and they were actually perfectly normal. Okay? Now those dogs were exposed to 454-fold the amount of moxidectin that a dog would be exposed to over one year. That is how much the level was in those dogs. Okay?

Now in studies prior to that, you don't just start a one-year study cold. You have to have previous information about how much you can give dogs so that you don't go over certain amounts. Okay? So in studies prior to that one, one-month studies and three-month studies. In those studies indeed at doses even way above the dose we used for the 454 multiplication factor, you would have the dogs showing the same thing. They would stop eating. Okay? They would have tremors. Okay? They would become lethargic, a very similar picture. But upon necropsy in those animals you don't see any systemic effects at all.

DR. AREF: But so it is likely if a dog was already compromised if you gave that injection without knowing it was compromised for whatever reason, it would not take that injection very well.

DR. BLASAK: Well, I can't speak to that. The toxicology studies were done in very healthy animals and I can't speak to whether or not if it is given to a compromised animal. I think it would certainly depend upon what is wrong with that animal to start with about what

would happen to the animal. Sorry.

DR. AREF: I have another question. It's about a couple pages further on. There is a field study mentioned on page 26 where client-owned dogs were looked at. There were 374 dogs representing 84 breeds. 280 were ProHeart treated and ProHeart 6 treated, and the others were -- 94 were on ProHeart oral tablets. On the next page they said that there were 12 other dogs were euthanized or died during the 12-month study, and those were all from the ProHeart 6 population. It doesn't say anything about any dog from the ProHeart oral population of these dogs. If none of the ProHeart oral dogs died, there is actually a statistical significance in the two populations' mortality rates at five percent.

DR. COBB: Dr. Rock, would you address that please?

DR. ROCK: Yes. We are talking about the field studies in the studies that you are talking about, and in conducting these types of studies a number of things happen. These studies are 18-month studies. Sometimes, you know, dogs would get hit by cars. They are not in there. Dogs, we had dogs that were lost in hunting accidents. We had dogs that ate antifreeze, and a number of different things that happened throughout the conduct of the field

trial. The bottom line in the interpretation of the experiments, both by Fort Dodge and by the FDA reviewers, is that these deaths could not be attributed to the use of the product, either the ProHeart 6 or the ProHeart tablet. ProHeart tablets at a very, very low dose, three micrograms.

DR. AREF: Based on the clinical observation, but it is assumed that the populations are equal except for the drug that they got? They should have the same kind of mortality rate, shouldn't they?

DR. ROCK: We find that in the conduct of this type of study and in the interpretation of these cases as I said, some were hit by cars, some hunting accidents. There was antifreeze. We did have, you know, two geriatric dogs. We had one dog that had congenital diseases which was talked about already today. But it was the interpretation that these -- that in both populations that there was not a correlation to the use of the product.

DR. AREF: Right. But I am just saying that just from when you have two groups of dogs who receive different drugs, there must be geriatric dogs in the oral ProHeart medication group and there must have been those that potentially could have been hit by cars and stuff. Were there none of those that were?

DR. ROCK: Yes, there were. I mean, there --

DR. AREF: There were ---?

DR. ROCK: Both populations basically reacted the same.

DR. AREF: Okay. Just because you mentioned only the 12 on the Proheart 6 --

DR. ROCK: No. The incidence was basically the same for both treatments. Remember the design of the experiment is two-thirds of the dogs are on ProHeart 6 and one-third are on the ProHeart tablet.

DR. AREF: Yes. It just doesn't say anywhere how many of the other ones died. That is the only -- I mean, because you don't give any numbers for those in the oral group that died then I was thinking that none of them died.

DR. ROCK: Okay. I understood we were writing the report for ProHeart 6 to provide you information like that, but the two populations basically responded the same.

DR. AREF: Okay.

DR. CRAIGMILL: We will move on and come back if you have one further. Dr. Bennett, I would like you to have 10 minutes now.

DR. BENNETT: Right. Thank you very much. I want to actually focus a little bit on the Banfield study a

little bit. The way I look at it from the FDA report there is about 12 million administered doses of the drug, and the Banfield people said they have administered about 735,000 or basically about six percent of all doses. What my concern was, my question was of the 485 deaths that the FDA has that are reported through the adverse event reporting system, how many of them come directly from the Banfield program?

Then secondly in general with this nice adverse event reporting system the Banfield field program has set up electronically, how many of those adverse event reports from the Banfield system when straight down to the FDA and when the FDA goes through their adverse event reports came out of the Banfield system? So just some cross-correlation between what Banfield reports and what the FDA reviews.

DR. NOVAK: So two questions, is how many --

DR. CRAIGMILL: Please identify yourself for the record.

DR. NOVAK: Dr. Will Novak, Chief Medical Officer for Banfield. Question one was I believe how many patient deaths did we have that were attributed to ProHeart 6. We had zero. And the second question was how many of the adverse events do we have that we have reported in our own system are then reported to either the manufacturer or

to the Food and Drug Administration. We don't of course have a requirement to report that through the system, and so I don't have an exact number. There are a handful of the reports that we've had that would have been reported with FDA. Anything that was reported with FDA goes through the normal reporting process. I am sorry -- have been anything that we reported would have been reported to Fort Dodge Animal Health. They have of course a requirement then to go ahead and report it on up through the system. And so any of the reporting that we would have done would have been something that we thought was above and beyond unusual after our peer-review process medical record review and that sort of thing.

DR. BENNETT: See, the question I have is given these several Dear Doctor letters and these package insert changes and the threshold for reporting decreased over time as I understand from what people said because awareness came up. It seems that if the threshold decreased over time then the original reports we heard from the FDA was that people would report differently at different thresholds. It seems to me a little strange that as those thresholds came up that the Banfield system didn't activate any different way than it had before, even though as you said up front that there was an increased alertness,

increased concern that these things might be related. That initially they might be passed off and then --- it might not have been.

DR. NOVAK: Okay. I am not completely following the train of thought there, but maybe to go through our adverse reporting system the way that we have got it set up is it designed for an interim reporting system. So we are then statistically tracking any variables that we would see for each of the individual components of the vaccine versus ProHeart 6. So we wouldn't particularly change the reporting methodologies going from us to let's say Fort Dodge Animal Health, unless we saw a spike on some change.

Now another example would be is that we may see a spike or a change on a vaccine, a particular component of a vaccine. That would then instigate that we would get involved with Fort Dodge Animal Health. Example, looking for a batch of vaccine that maybe we think needs to be changed out. So, and I'm not -- the reporting system, I do have the same concerns about the general reporting system when it comes to everything that has been discussed today is that by nature if you send out a Dear Doctor letter one would have a heightened concern about some things. We have an internal medical advisory group that fields a lot of

those questions, and so we are -- we got a lot more interchange between board-certified experts at our main office and our doctors in the field. So, you know, we are constantly looking at this thing internally.

DR. BENNETT: Well, okay. I won't go belabor the point, but the last point I would make is that if you had a concern about the way the cases were adjudicated between what you saw or when you reviewed the FDA reports and there was concern that Fort Dodge didn't adjudicate them the same way as the FDA did when there were cases to be adjudicated. My question was why don't they look at the exact same cases that you have in your data set that the FDA has and adjudicate them to see if you get concordant or discordant reasons and discordant things. You could adjudicate those even with what they have by matching them up by state and dog size or something like that. There are some ways that --- but you are also going to report.

The last thing I wanted to bring up is the question that was brought up from one of these speakers, was the issue about the handling of the product. I think that is a point that I think when I look at the side effects of ITP, IMHA, anaphylaxis, it raises a concern to me again of the question of the single vial that somebody brought up as an issue as opposed to the repeat use vial. Any questions

about impurity related to not actually the product, the drug itself, but the vehicle and the stability? And I am wondering if the company has spent some energy to look at the stability in terms of multi use as opposed to single use and whether these adverse events that have been reported are associated with vials that have been potentially out there more with more environmental exposure than the other vials.

DR. COBB: I would be happy to address that question. Yes, the company has expended a great deal of time and effort looking at various aspects that you raise and they are very valid aspects. When we initially received reports after the product was launched we in fact did a number of practice surveys because we did notice a cluster effect in that a practice in one city may report several reports. Neighboring practices did not report any. And our first thinking was there may be something in the handling, the storage, or the administration of the product. In fact, people from our professional services and research groups went out and visited practices, spoke to the veterinarians, to the technicians who were involved in handling the product. They even spoke to some of the pet owners to try to understand if there was any identifiable predilection that would point us to something that precipitated a reaction. We were unable to identify any patterns.

We certainly have conducted extensive stability testing on the product, both in its primary presentation as two vials and also in its reconstituted presentation. That has involved repeat penetration of vials. It's involved storage of inverted vials versus upright vials. We find that the product can be stored under normal usage conditions according to the label without any detectible deterioration or change in the product. We certainly have looked at what happens to microspheres over time, whether there is different release of moxidectin as the microspheres age. We do not find that in our testing, and I think a comment was raised about the coating on the microspheres. I would stress we don't coat the microspheres. The microspheres are manufactured from a consistent granulation to insure a uniform distribution of moxidectin through the glyceryl tristearate matrix.

As far as the carrier, we did extensive testing on the hydroxypropyl methylcellulose. We sent quality assurance auditors into the manufacturing facility to see if there was any possibility that the product could be contaminated either during manufacture with something else that was being produced by that manufacturer. The quality audit was very favorable. All of our stability tests, sterility tests, have shown that the product when

used and stored according to label and under the rigors of normal commercial use appears to be very stable. We brought product back from the field. We tested it extensively, product where dogs had been treated with that particular vial and had reacted, and we could not determine any deterioration or change in the product that we could attribute to a reaction.

DR. CRAIGMILL: If I may just interject one question here. Thermal stability, did you test that? I'm sure you tested thermal stability of the preparation of the microspheres, and could you comment on thermal stability if perhaps something got a little too warm?

DR. COBB: Thermal stability is an issue, and at above 40 degrees centigrade there can be a change in the matrix of the glyceryl tristerate. Moxidectin also is temperature sensitive. It is a fermentation product and like many fermentation products is temperature sensitive, and temperatures above 60 degrees centigrade would be expected to cause some degradation of moxidectin. They were not temperatures that we encountered in our site visits to the practices. The products generally were stored according to directions. We found reconstituted products generally were stored in refrigeration or at worst sat on a bench top for several hours. They were not exposed to temperatures of

60 degrees centigrade that we could determine.

DR. CRAIGMILL: Okay. If I may follow it just a little bit more. So the microspheres may become unstable if they are heated greater than 40 degrees centigrade?

DR. COBB: The microspheres may actually change their physical form a little bit. The glyceryl tristerate has a critical temperature of 40 degrees C, and does change into a slightly different form and you may see clumping of the microspheres if they are heated to greater than 40 degrees. That was one of the first things we looked at when we did our field visits to see has this product been heat stressed, are the microspheres a conglomerate in the bottom of the vial rather than being free-flowing microspheres, and we did not find that.

DR. CRAIGMILL: So there is a visual representation that you can see. It is a very visual --

DR. COBB: It is very visual. They actually glue together in a big blob.

DR. CRAIGMILL: And so you can possibly give it if that had happened in shipping or anything like that?

DR. COBB: They would need to --- I think.

DR. CRAIGMILL: Okay. Thank you very much. That is what I was wondering. At this point, I would like

to move to another one of the people who has not spoken yet, Mr. Jaffe.

MR. JAFFE: Okay. Thank you very much. I have a question for Fort Dodge. The report that we were given that you had produced talked about incident rates of adverse incident reports in -- 10,000 doses sold. It was a rate as to 10,000 doses sold. I guess I would like to know whether you have some information about how many dogs were actually give ProHeart over the two-and-a-half years that it was marketed and whether you have done any calculations of sort of rate per 10,000 dogs for example. I know that some of these adverse incidents you would expect if they had multiple doses the chance of the likelihood of it happening to be decreasing and so forth. Allergies and so forth if they had gotten through the first dose without any adverse incidents. So I am curious if you can tell us what information you have in terms of how many dogs have actually been treated with ProHeart, how many dogs are repeat in terms of the number of doses per dog that have been gotten since the product has been on the market.

DR. HUSTEAD: You ask very interesting questions. The numbers of doses of ProHeart which have been sold are about 18 million. We estimate that about 12 million dogs have been dosed with the product. We get that

from interviews with our customers and analysis of marketing data which comes into the company. We have not calculated a rate of adverse event report per that number because the number is so highly skewed we don't know how to evaluate it. So as has been presented, you need to be very careful when you look at incidence rates so that you can draw any sorts of conclusions with them. One of the things you have to do is have consistent numbers, and the numbers of dogs is just not a number that we can get a hold of with any consistency.

MR. JAFFE: So the numbers that are in the report are done on the 18 million figure, not the 12 million figure?

DR. HUSTEAD: They are the number of doses sold. That's correct.

MR. JAFFE: Okay. Thank you.

DR. CRAIGMILL: Anything else, Greg?

MR. JAFFE: No.

DR. CRAIGMILL: Okay. Let's move then to Dr. Nolan.

DR. NOLAN: Hi. I wanted to ask Dr. Brown about the Fort Dodge assessment of -- how if you tried to reconcile what they found as remotely related to ProHeart to your possibly related.

DR. BROWN: Well, I didn't really participate

in training Fort Dodge in the use of the algorithm, so I'm not sure how consistently it was applied. But something that has to be considered is the initial categorization as to assigning something else as a possible etiologic agent. We apply that to the algorithm, which is weighted to take all of that into account. So that as you go dog by dog, drug by drug, clinical sign by clinical sign, you have the same consistent type of score that -- for a causality assessment that can be reached. If one considers only that there is something else that could be causing that and therefore you say it is unlikely or remote, then you don't apply that to the weighted algorithm. You simply take those out as unlikely and exclude them from the beginning.

DR. PETERSON: I have a question for Dr. Glickman. The study that you did with the Banfield, you set up three groups of dogs that were on heartworm preventive to include the ProHeart 6. Did you examine whether or not there were any differences in the basic demographics among those three groups? For example, age, breed, or gender?

DR. GLICKMAN: Qualitatively there were no differences. If you apply statistical testing to them, there are statistically significant differences, not surprising given the sheer number in some of those groups of 700,000 or 400,000. You get very significant P values, but

clinically no. You are talking about perhaps a percentage of females of 52 percent versus 50 percent, but they come out. You know, you traditionally look at it and say, "Oh, wow. Statistically significant." But I didn't see any clinical significance of that magnitude of difference.

DR. PETERSON: Okay. Thank you.

DR. SAMS: Thank you. The preparation of the formulation for injection involves a number of steps that are specified in the product insert, and those steps appear to me to be somewhat more involved than for the preparation of other parenteral formulations that are on the market. Therefore it seems to me that there are opportunities for error in the preparation, administration, storing and handling of the product. So my question is, have any studies been done involving the intentional mishandling in terms of either of the preparation, administration, storage, or administration of the product?

DR. COBB: In terms of the detailed instructions for reconstitution, they are there for a purpose because this product is a little different than a reconstituted solution or a reconstituted suspension that is used in a single treatment. We do have an approved shelf life of one month for reconstituted product in the US. So it was very important to us to write detailed instructions

to be sure that this product could be used safely and effectively within that time window. In some other markets are reconstituted shelf life has been adjudged to be two months.

We certainly looked at what happens if you do it differently. If you use too much diluent, and we do put a little overage of diluent in the vial to allow the veterinarian to express any air bubbles that he may draw into the syringe. You may a product that is marginally more dilute. If you lose half of your diluent, if it squirts out of your syringe, you may reconstitute a product that is somewhat more concentrated. But certainly our --- studies with ProHeart 12 show that three times the concentration can be administered and used with safety in dogs.

There were questions raised as to why do we recommend that the product be swirled after reconstitution, are the microspheres so fragile that if you shake the product after constitution is this a problem. The reason we saw swirl rather than shake is that if you shake it you end up with a lot of air bubbles in there, and it means then that you have to put the vial down and let it sit for perhaps 40 or 60 minutes to allow those air bubbles to release themselves from the formulation. That obviously

would be a significant irritation both to the client and the veterinarian. So we do recommend that you make sure that the microspheres are uniformly suspended by that gentle swirling. But, yes, the product has been fairly rigorously tested in terms of what we would expect to happen under normal field conditions where people do get the dilution rate wrong or they go to inject the dog and some of it squirts out and the dog is under-dosed. We've looked at that.

DR. SAMS: Can any of the adverse drug reactions be attributed to any mishandling of the product during its preparation, administration, or storage?

DR. COBB: We have looked very meticulously many times, and we have not been able to identify any adverse event related to drug mishandling or poor storage by veterinarians. No.

DR. SAMS: Does Banfield conduct training programs specifically directed toward the preparation of this product?

MR. : Will, did you hear that question?

DR. NOVAK: Yes. The question is do we have specific training programs; and, yes, we do.

DR SAMS: And is that program applied

uniformly across all of your sites?

DR. NOVAK: We believe so. As with 1,000 veterinarians you will always have a little variation.

DR. SAMS: But there is a formal program?

DR. NOVAK: Yes. We have a web-based training program as well as when we originally launched the product we did regional meetings. So we spent a fair amount of time making sure that all of the steps of the process were well trained against.

DR. SAMS: Thank you.

DR. CRAIGMILL: I guess it is my turn. I have a slide for Dr. Brown -- slide -- question for Dr. Brown. I would like to hear what the FDA knows about the Australian experience with the ProHeart 12 drug in terms of two major questions. One, is their adverse event reporting system similar to ours; and, two, what is there experience with that drug?

DR. BROWN: Well, it is my understanding that in the different countries around the world that the adverse event reporting systems are actually somewhat different in terms of their collection and the way that they are interpreted. Perhaps Dr. Post as Chairman of the VICH might be more prepared to answer that.

DR. POST: Well, I will beg off on the VICH

part, but it's just different. Different populations, different systems. It's about it.

DR. CRAIGMILL: Can you comment about what they have found, seen, or in terms of have they had a similar problem basically or any of the other countries where it is approved?

DR. POST: No, I can't really comment on different countries, what they have found or haven't found. I just know about what we found in the US.

DR. BROWN: I would just have to refer you to the websites for those countries and to take a look at the numbers of reports that have been received and what types of reports they are.

DR. CRAIGMILL: Just even one further question about obfuscation. Do you know is the formulation the same as -- it is a different formulation being used, right? Or is it a different carrier?

DR. BROWN: I would be happy to answer that. The formulation in fact is the same. We put three times as much mircospheres in the microsphere vial. We put the same amount of diluent in the diluent vial. So the product is administered at three times the does, three times the concentration, but at the same volume.

DR. CRAIGMILL: Yes, Dr. Hustead?

DR. HUSTEAD: Well, I am actively involved in the Australian adverse event regulatory arena as my area of responsibility is all countries around the world. And it is my assessment that the adverse event reporting system in Australia is actually very similar to the FDA's reporting system. There are of course always differences, but those differences are comparing vanilla ice cream and French vanilla ice cream. The similarities are much more similar than the differences. And as far as the adverse events that they have experienced, it is our review of the events in Australia and here that they are highly similar

DR. CRAIGMILL: Okay. Thank you. My second -- I have four questions, and we will take a break at 3:00. My second question has to do with we heard about the long-term studies that have been done with moxidectin per se. I would like to know what acute and chronic studies have been done with the actual formulations, multiple injections, one, three, five-X doses, et cetera, for ProHeart 6. Can we have someone to cover that?

DR. COBB: Yes. I will ask Dr. Rock to cover that.

DR. ROCK: The safety program for ProHeart 6 actually covered three types of studies. The first type of study is a safety study in the target animal. Okay? It's a

one, three, and five-X study, and there is a necropsy of high-dose and then controls. If there is something for us to look at, if there is a trend or something there, then we will go in and do the mid doses.

DR. CRAIGMILL: Can I clarify? Is that a single dose?

DR. ROCK: That's a single dose. Yes.

DR. CRAIGMILL: Thank you.

DR. ROCK: Okay. We have also done a study in ivermectin-sensitive Collies. In that study we choose Collies which are shown to be sensitive to 120 microgram dose of ivermectin. That's approximately a 1X dose for a 20 KG dog. We use a 1X, a 3X, and a 5X in that study, and we follow those dogs for two days. We are looking for typical signs of toxicity which would mainly be CNS effects. We follow those dogs in locomotion studies, and we also follow immediate reactions to those dogs, and in that study we saw none.

In a third study which was already talked about today, we identified dogs that are naturally infected with heartworms. We determine that by measuring the circulating levels of microfilaria. We then treat those dogs with a 3X dose, a single dose of ProHeart 6, and then we necropsy those dogs later on and look for abnormal

reactions. We are also looking for abnormal reactions immediately after treatment. If there is some of the toxic effects that one might expect if we were having a mass kill of adults, and allergic reaction or something to that nature, and in those studies we were -- we did not show any adverse reactions.

Just one step further in our discussion as part of -- and Dr. Cobb talked about it earlier today, as part of the ProHeart 12 program we did do a heartworm-positive study with dogs that had 20 adult heartworms inserted via the juggler vein, and looked at adverse reactions. In those dogs we let those worms equilibrate for a period of 60 days I believe, and then we treated them with a 3X of ProHeart 12, which was a 9X of ProHeart 6, and there were no adverse reactions in that experiment as well.

DR. CRAIGMILL: Do you have data from multiple injections of the ProHeart 6 in dogs?

DR. ROCK: We have a small, non-pivotal study in multiple injections. It was in -- it is in the FOI where we started out -- one of the concerns that we had at the beginning of the development program with ProHeart 6 was if we are going to have dogs on ProHeart 6, two injections a year for a period of seven, eight years or something to that nature, what is going to happen with each one of those

injection sites? So we set up a study which starts out with a fair number of dogs, but at each time point after six months, after 12 months, throughout a period of time, we will necropsy and excise those injection sites in a small number of dogs. Whether it is two or four, we will go left side, right side, both on the right side, and all different combinations. It ends up with a large number of dogs, but it ends up with a small number of dogs at each of the necropsy points if you are trying to cover all points. In that study we determined or we observed that there was no adverse reaction to multiple injections, nor was there any accumulation of the drug in the body.

DR. CRAIGMILL: Okay. Being a toxicologist, one more question. Did you run a test of the formulation using like a guinea pig, hypersensitization model, anything like that as part of the initial acute screen?

DR. ROCK: There were these types of studies way back in the discovery phase when we were dealing with moxi

-- with microspheres as a whole, and there was -- we did not identify any problem with the use of microspheres.

DR. CRAIGMILL: Okay. I will save my last two questions until after break. We will come back and recommence at 3:15. Sorry. Aleta has something for now.

MS. SINDELAR: I am sorry. Just for the purposes of transcription and for the record, Dr. Tuttle has agreed to just make some comments which he didn't make at the opening of his five minutes.

DR. TUTTLE: I apologize. I didn't announce. I have no financial interest with Fort Dodge, a general drug distributor who provides not only Fort Dodge products but all of our other products did pay my expenses here.

DR. SINDELAR: Thank you very much. Okay, 15 minutes please.

(Whereupon, a short break was taken.)

DR. CRAIGMILL: Okay. At this time I would like to ask Fort Dodge Animal Health people again and Dr. Cobb probably and who will probably refer it to somebody else again. It is a follow-up question to Dr. Papich's question about the pharmacokinetic values. You mentioned the Tmax, the time of maximal concentration was somewhat variable. The key point I believe five and 14 days? The Cmax, the actual concentration obtained, what type of variability did you see with that?

DR. COBB: The variability in the Cmax is not enormous. It ranges generally around the order of five nanograms per ml, but we do not see levels in excess of six. So it is quite tight Cmax, although the Tmax may vary a

little bit in individual dogs.

DR. CRAIGMILL: So you don't see why it swings in that, in the Cmax at all. Interesting. Thank you. Dr. Nelson, whom I cut off at lunch, now we will return with his questions.

DR. NELSON: Aa a clinician, I am more concerned about clinical cases, and I would kind of like to return to these cases that were presented to the committee as representative of some of the problems that were going on. I guess one, the liver, since Dr. Brown was bring about the pathology of the liver in these six cases, one of the things here, there is only one case that actually has a level of what the ALT was. Mostly it says it's elevated. Did you get actual, you know, values on these cases? Or the report just came in elevated ALT?

DR. BROWN: That would depend. In most of them I would say that we do have actual values, and there again they are considered elevated reported by the veterinarian who is attending clinical that patient and also referring to the baseline of the laboratory that that individual practitioner uses.

DR. NELSON: Then also in those cases two were necropsy, one had a biopsy. You were asking about pathology, and the third case we get a biopsy, and this done

like three or four days after the injection. The diagnosis came back as chronic active hepatitis?

DR. BROWN: Yes.

DR. NELSON: And then on another case, case number five, necropsy was approximately two weeks after injection, and in that one there was some mineralization in the kidney tubules, which is more of a chronic kidney problem? I guess one of the --- today with these clinical cases is the lack of information. In the neurological cases one of the things you had in here on case number six, you talked about a CSF tap and then you bring up a distemper titer of one to 80. Is that in CSF fluid or one to 80 in serum?

DR. BROWN: Oh. I believe that was in the CSF fluid.

DR. NELSON: Which positive titer and CSF fluid is pretty much indicative of distemper, right?

DR. BROWN: Well, the laboratory said that could indicate vaccination infection or exposure.

DR. NELSON: Did you have the titer of also serum?

DR. BROWN: No. That’s the only titer we have.

DR. NELSON: Also there are some questions in

here about health status?

DR. BROWN: Yes.

DR. NELSON: I thought it was interesting that it listed health as good in a 40-pound Dachshund?

DR. BROWN: Oh. Yes, I found that rather interesting myself.

(Laughter.)

DR. BROWN: Actually in that circumstance obesity would be listed as a concomitant medical problem and for circumstances anything affected cardiology or the joints or the liver we would of course give that a -1 in the alternate agent category.

DR. NELSON: The other thing that is also not listed, and you talk about concomitant use of vaccinations, it just says distemper. It does not list whether it is distemper with lepto or without. Do you have any of that information?

DR. BROWN: Yes, usually we do have that information, and for almost all of these if it says it is distemper vaccine it is actually referring to distemper adnovirus parvovirus combination. Usually with lepto unless specified not.

DR. NELSON: So all the ones that say just distemper you had lepto included?

DR. BROWN: Yes. In some circumstances we have the actual names of the vaccinations used, and in others we don't.

DR. NELSON: And then also did you have, as I brought up earlier, any information about previous heartworm preventatives in a lot of these cases where there's gaps of two years?

DR. BROWN: In many of them we don't. Sometimes we have owners coming to practices with all their previous records in hand. Sometimes they will come and there is really no previous information available. If the reporting veterinarian has been able to ascertain that, that would be in the medical record, or we might call them and ask them for that information. But if they don't have it, then they just don't have it, and that does kind of obscure the possibility of has there been a repeated exposure or has there been the possibility of a cross-reaction across a class of the macrocyclic lactones. We are just not able to say in those circumstances.

DR. NELSON: Well, I hate beat a dead horse, but the whole issue of heartworm status is so important with these drugs. I mean, there is not one of these drugs that we have not seen reaction in a heartworm-positive dog, and then just the whole understanding of the pathogenesis of

heartworm disease. It was a little disturbing in going through the CVM's report referring back to the 1999 guidelines and about heartworms being found in the right atrium. When they break loose there it is supposed to be in the pulmonary artery they are found, and also the three-month disease cycle that we actually have two-inch worms in pulmonary arteries at 90 days. So it is extremely important that the heartworm status of these dogs and the prior preventative that has been administered be known if you are going to try to predict any type of anaphylactic reaction to --- filaria.

DR. BROWN: Yes. We really would like to have that information, and as I said many times we have called and asked please go back and try to find it. Often they will send the entire record that they have to us, and it is just not there. It really would be helpful if we had more complete reporting.

DR. CRAIGMILL: Other members? Dr. Brown.

DR. C. BROWN: I have a follow-on to that. Not to sound like a little dog at the end of a rag, but necropsy findings, histopathology, is there any further data on that to be presented?

DR. HARRIS: I'm Keith Harris. I'm head of pathology for Wyeth Research. I will try to talk loudly --

MR. : --- will get the microphone.

DR. HARRIS: Is that better? I'm Keith Harris. I'm head of pathology for drug safety in Wyeth Research, and I guess this goes back to your earlier question of how many necropsy and pathology reports we had in the Fort Dodge database, and there were -- out of the 616 animal in our database, there were 165 necropsies. Out of those we had eight -- there were 85 pathology reports, and to the best of my knowledge all the pathology reports went to the various consultants that were looking at liver, CNS, immune-mediated disease, and that's how we divvied them up. So I focused for example on liver, and I did look at a few heart cases as well. Does that answer your question?

DR. C. BROWN: So you read the reports, but you didn't review the series of slides?

DR. HARRIS: No. The only ones we read, the -- we looked at the reports, looked at -- in my case I looked at -- we all looked at the total package, but we looked at the reports, looked at what the individual diagnoses was made by the pathologist, then looked at their final comments. The only case that I looked at slides or did we look at slides was in two heart cases where I looked at sections from the animal in trying to figure out what was going on in the heart.

DR. C. BROWN: Thank you.

DR. GROSECLOSE: Just a question on the series of studies that were discussed just prior to the break. I had wondered whether those were done pre-marketing or post-marketing, and how many animals may have been included in those studies, and what was the power to detect any adverse events in those studies should there have been any?

DR. ROCK: The safety testing was done during the development program, and it is done to a standard design that was discussed with the Center for Veterinary Medicine prior to initiation of the development program.

DR. GROSECLOSE: Okay. Maybe I can then direct it at the Center for Veterinary Medicine. What power do those studies have based on the sample size that you require to detect adverse events prior to bringing these biologics to market?

DR. POST: We don't do a statistical analysis. It is all -- oh, are you talking about pre-market?

DR. GROSECLOSE: Pre-marketing, right.

DR. POST: I'm talking about post-marketing. I will defer that question to Dr. ---.

DR. BARTHOLOMEW: I will try to address it, and the answer to that --

MR. : Please identify yourself.

DR. BARTHOLOMEW: Mary Bartholomew from the Center for Veterinary Medicine. I'm in the biometrics group and we review target animal safety studies for the Center. The gentleman from Fort Dodge Animal Health is correct in that there is a fairly standard study design that has been used for companion animals, and the typical study size is four males and four females per treatment group in each of zero, one, a three, and a five-X study. The reason for using the exaggerated doses is typically because the studies are fairly small and we are trying elicit the toxic syndrome. So in terms of power we'd have to talk about what size difference for what variable, and we look at sometimes for including all the clinical chemistry, the hematology, necropsy variables, and some of the in-life measurements like weight and feed consumption. We look at probably 50 variables, so there is also a multiplicity issue there. But that is the typical size. Sometimes that varies, but that is the standard-sized study and I believe that's the size study that Fort Dodge did.

DR. GROSECLOSE: Okay. Thank you. Just two more questions. The microsphere technology, is that used in

any other of your biologics at Fort Dodge?

DR. COBB: No. We do not use that microsphere technology in any of our other products.

DR. GROSECLOSE: And a question for Dr. Glickman. Could you review the findings of your multivariant analysis of the association between ProHeart and allergic reaction? There seemed to be a statistical -- I mean an increased risk of allergic reactions in dogs that were administered

ProHeart 6, and you didn't mention it in your conclusions, and I --.

DR. GLICKMAN: Yes. In looking at the multivariant model, well, what we saw from just looking at rates was that there appeared to be an increased rate of allergic reactions in the dogs that got vaccine compared with the dogs that got any of the heartworm products. In fact, this came out in multivariant analysis. There was this 150 percent increase in the risk of allergic reaction in vaccinated dogs versus not vaccinated. Both ProHeart and heartworm one monthly also were associated with an increased risk of allergic reactions. In ProHeart it was increased 38 percent, and heartworm one 12 percent. We probably didn't see any increased risks for heartworm two because it is the more infrequently used product, so the sample size was much

lower. Had the sample size been bigger, we probably would have seen an increased risk rate as well. So we did see an increased risk of allergic reactions for basically all of the heartworm preventives we studied, of course as well as with steroids because of this use association.

But the interesting thing to me was then if you look at each additional dose of ProHeart, the risks do not go up further. In fact, it was marginally reduced.

DR. GROSECLOSE: Well, how did you account for say -- I don't want to belabor it, but, you know, a dog that had two versus three versus four in your model?

DR. GLICKMAN: Well, we put that in, in the model. One dose, this was ---. Zero would be no dose, then first dose, second dose, third dose, fourth dose, and it went in the model just that way; and there was no significant dose response relationship on the up side, and even on the down side. It was sort of a negligible change in risk with each additional dose.

DR. GROSECLOSE: Did you see any dogs that may have received one dose of ProHeart who then received -- went back to a monthly heartworm medication subsequent to the first dose?

DR. GLICKMAN: No, we didn't track longitudinally in this case and distinguish reactions to see

if a reaction on the first dose would be associated with a reaction on the third or fourth. It's interesting. We have done a large study in this database with vaccines, which appear to be more allergenic, and sort of the belief out there is, "Well, if a dog has an allergic reaction to our vaccine, either you shouldn't give it again or you have to pretreat or whatever." And using this database we have seen no larger risk with a second dose in a dog that had a reaction the first time than in a dog that did not have a reaction the first time. This is the first time we have been able to look at this scientifically, and pretty much we are finding similar things with ProHeart. It was a little harder with the oral monthlies because since they weren't given in the practice it is harder to track, and owners miss doses and you would probably not know about that if there is no way to track it.

DR. MEALEY: Okay. One question about the mast cell tumor, the increased risk that you found with mast cell tumors. Were any of those mast cell tumors found at the injection site?

DR. GLICKMAN: That's a good question. We have not gone back to look at two things, though clearly one should know whether it is at the injection site or not, and, two, whether perhaps histopathologically they differ, that

is mast cells in dogs that got ProHeart versus mast cells in dogs that did not get ProHeart. For example like we see with fibrosarcoma in --- when they occur at injection site they are much more aggressive, et cetera, than if they are not. That has not been done.

What we did do was to calculate how many dogs would we need in a prospective study. For example, to detect this increased rate that you see with let's say ProHeart with vaccine versus vaccine alone in the incidence of mast cell tumor, and it comes out to be 600 --- dogs per group, so it is clearly never going to be done.

But what you suggested is absolutely right. One should go back now and for those dogs who have histopathology, which most will, actually pull them out and compare them, and also try to get more information on the site of the tumor, which we did not do. Phil, do you want to say more about the medicine?

DR. BERGMAN: Yes. Dr. Mealey, in reference to your question, my name is Phil Bergman and the outside oncology consultant for FDAH. Of the 130 cases that we had available that I had available to review, there were three dogs with mast cell tumor, and none were associated at the injection site. Importantly, all three of those dogs actually had their tumors occur with three weeks of

injection of ProHeart 6. So suggesting that there was no association with ProHeart 6.

DR. MEALEY: Second question is there seems to be a concern, and I have some concern, that maybe moxidectin itself as the drug is maybe not a cause of these adverse events, but potentially the vehicle. And in the FDA documents that we got on page 11 there's a couple of statements in there about letters that were made from the FDA to Fort Dodge Animal Health about problems with manufacturing. There was sterilization problems I think and dissolution time point and GMP violations basically. I guess I want to know, is that a fairly common -- are those letters, citations, whatever they are, are they fairly common among manufacturing pharmaceutical industries, or is that kind of an unusual thing?

DR. : I don't know if I can answer how common they are, but it is these letters were not really directly connected with adverse drug events. They were just some manufacturing problems that were cited in an inspection.

DR. COBB: Perhaps I can comment on those issues. The first issue related to dissolution testing failure. Dissolution testing is conducted under laboratory conditions, and it measures the consistency of a product

release. We put the product into a laboratory media and we measure how much moxidectin is coming out at 1.0 hour, 1.5, 2.0, 2.5, and 4.0 hours. Every batch of ProHeart 6 that is released passes that dissolution test before it can be released.

On one occasion we did test some six month stability samples that had been stored for six months and had already been released, and we found that these two batches which were made from the one lot of microspheres marginally failed our dissolution specification at 2.0 hours and 2.5. The release specification was within specification at the 1.0 hour and 4.0 hour time limit. Despite that, it did not make specification. We recalled those batches from the market.

However I would say to you that this is a manufacturing consistency test. It tells you nothing about how the product releases in the dog, and certainly a dissolution test that showed a slightly slower release at two intermediate time points over a four-hour period would not be expected to have any clinical impact.

The second issue in relation to the plant inspection and the warning letter, I might ask Mr. Corcoran to comment on that. I believe that all of those issues have been resolved and much to the satisfaction of the FDA.

MR. CORCORAN: Yes. I'm Tom Corcoran with Fort Dodge Animal Health. Countering along with Dr. Post's comment, the warning letter we received is the first warning letter that we have received in at least over 10 years that I am aware of. Previous inspections have been absolutely spot on, very few observations. We were having an inspection in December of 2003. The observations were mostly administrative type of observations. We undertook a full retraining of our personnel, underwent an inspection in October of this year and got a complete bill of health from the FDA.

DR. LUSTER: A couple of quick questions. You talked about immunogenicity testing earlier and said you had done it, and I saw the post-clinical data presented in the document. But what preclinical immunogenicity testing were you referring to? You indicated you tested the moxidectin separately and the microspheres separately. Did you test the formula as it is used together?

DR. COBB: Yes. In our testing what we did was we ran a large number of tests. Tests were run on the complete product, on the microspheres containing moxidectin component, on the vehicle alone, on microspheres that did not contain moxidectin, and we ran it independently on various components of the vehicle. The vehicle carries

several preservatives,

--- and ---. They are preservatives that are commonly used in human and veterinary pharmaceuticals. We have looked at those. We have looked at the hydroxypropyl methylcellulose, and so that we did run tests on the individual components as well as the microsphere component and the total product as well.

DR. LUSTER: What was the test that you ran?

DR. COBB: We ran a number of tests. We looked at IGE and IGG levels in dogs that had reacted and could not find any evidence that these reactions were mediated by gammaglobulins. We did passive cutaneous hypersensitivity testing and had very mixed results and not repeatable. We did intradermal skin testing again with very mixed results and not repeatable.

DR. LUSTER: So this is preclinical dog studies that you are doing this immunogenicity testing on you are saying?

DR. COBB: These were actually done as a result of field reports of adverse events, but they were done in laboratory settings.

DR. LUSTER: And also a little bit of clarification, but regarding the -- I was a little confused because the FDA people were talking about an increase,

showed some data in their talk as an increase in anaphylactic responses after they were adjusting for market shares. Then you were talking about a decrease in anaphylactic responses, or equal amount of anaphylactic responses with ProHeart as there is with vaccine responses? Can you clarify that for me? Is it more or less? And this is data without obviously concomitant vaccine data.

DR. BROWN: Are you asking us initially?

DR. LUSTER: Yes. I would ask you first.

DR. BROWN: So you had wanted to know if we felt that there was an increase in reactions, anaphylactoid reactions after --

DR. LUSTER: Well, you indicated that there were -- after you adjusted. In your talk you adjusted for usage or for market share, and you said that the actual rate of increase in anaphylactic responses in dogs that took ProHeart without vaccination was three-fold or something like that? Is that -- did I get that number correct?

DR. BROWN: I think we might be talking about several different things. One reference I made was to adverse events, full anaphylactoid events over the marketing years, and we felt that there was a decrease in those number of events after the label change in June of 2002. Although we still do have a significant number of events. That was

one factor.

I think the other was in Dr. Post's slide when he was showing you the effect of was there a reduction in serious events after the minimum residue solvent lots were put into the market, and he was showing that in fact there were not. That we were continuing to receive high numbers of serious events, even after those lots with minimum residue solvents were in full market.

DR. LUSTER: I know you are being very careful and not saying any numbers, but you did mention numbers in your

-- at the conclusion of your talk.

DR. BROWN: Oh. That may have been when I was referring to the Fort Dodge document? Talking about anaphylactoid -- about allergic reactions with vaccines versus ProHeart 6?

DR. LUSTER: Right.

DR. BROWN: Okay. Yes, that was referring back to Fort Dodge's narrative that they submitted in which they showed that the reaction rate was I believe 1.16 -- 1.62 with -- sorry, 1.26 with ProHeart 6 versus 0.4 with the Duramune distemper vaccine or a 0.5 with the Rabvac 3 vaccine. Is that --?

DR. LUSTER: That's right.

DR. BROWN: Right. Which makes the reporting allergy event rate for ProHeart 6 two-and-a-half to three-and-a-half times higher.

DR. LUSTER: Well, that is how you got that number. Okay.

DR. BROWN: Right. That is on page 11.

DR. LUSTER: Okay.

DR. BROWN: That is on page 11 of my slides, but it is on page 37 to 38 of Fort Dodge's narrative.

DR. LUSTER: Okay. Now in the Banfield study, the Banfield spokesman said that you saw approximately the same amount of anaphylactic responses with ProHeart 6 as you did with vaccination. Is that true? Anaphylactic responses.

DR. GLICKMAN: Yes, the rates were extremely low, 0.7, 0.4 per 10,000. So they were extremely low for any of the products in terms of anaphylactoid. Not for allergic.

DR. LUSTER: Just that it is easy. As I indicated earlier, it was easy. It's easy to say this is allergy if a dog has a skin reaction and the dog has anaphylaxis. It is more likely to be reported I would assume, and it is quite a bit more obvious.

DR. GLICKMAN: Yes. I think in general

regardless of which, even the passive reporting, and certainly interactive review of the records. Reactions that occur within the first one, two, three days, are much more likely to be reported than reactions that occur later on because of this association in time between the event and the product. You know, just mentally one is less apt to associate the two. So there is much more complete reporting I think for early events than there is for later events.

Interesting, too, when you look at the -- you mention the allergic event rate of 1.26 that was calculated by Fort Dodge from passive reporting. In the Banfield database we calculate a rate that is roughly 18-fold higher, and that is the first time maybe where we have a comparison of -- or a basis for stating what the amount of under-reporting is in a passive system, and that is in a reaction that is more likely to be recognized. So under-reporting, yeah, it might be harder for the others that occur late.

DR. HUSTEAD: I would like to clarify as well that the number of adverse event reports in the allergy category are going down each year following 2002, and there relative frequency is also decreasing as well.

DR. NELSON: I have one more question. I skipped over this earlier. Dr. Cobb, you all talked about certainly

microfilaria were cleared approximately one week after injection, and you know the effect against three month and four month old. Do you have an data of actually how rapidly L3s, L4s, and L5s die?

DR. ROCK: In our heartworm-positive study which we conducted with naturally-infected dogs there was a 97.6 percent reduction in circulating mircofilaria at seven days, which increased to 98 at 14 and 99 from there on out through a 28-day study. One has to assume that if they are naturally infected dogs that those stages of larvae would be part of that population. If you look at the three- and four- and six-month-old infection study, the retroactive studies where these animals are being infected with microfilaria, the microfilaria are allowed to mature for three to six months. Some of those microfilaria, those larva stages are going to be the stages that you are concerned with, too, and there was no as we discussed previously in a previous question, there was no adverse reaction in those dogs as well.

DR. NELSON: I guess the question I am asking, do you know how long after the administration that you actually start to see like an L5 die?

DR. ROCK: I don't have that exact number. No, I don't.

DR. NELSON: I was just trying --- correlation with, you know, being a clinical science or not.

DR. ROCK: True.

DR. RIDDELL: I guess I have a couple of relatively disparate questions. Another thing that I do, I am involved with AVMA's Council on Biologic and Therapeutic Agents. Currently I am being chair of COBTA, and I appreciate Dr. Glickman's information about the relative reporting rates. That is something we have been looking for. COBTA has expended not a small amount of effort in the last couple of years to enhance adverse event reporting by the practitioner through the USP network and to FDA and also working with the Center for Biologics as far as vaccines. We have also been working with that National Animal Poison Control Center.

I guess I have and AVMA has always asked for a lot of these decisions to be made based upon science, and it is a little bit frustrating to me. We are having to ask people to make very weighty decisions with not a lot of science out there floating around. So I am very intrigued by the potential power in a database like Banfield's, and I had a question for I think probably Banfield.

Is when an adverse drug event is reported, there must be a team to evaluate it, and if so at what point

will a trigger point be reached that that would be reported to the sponsor, whereupon it would have to go to FDA?

DR. CAMPBELL: Any adverse event at all, you know, is reviewed by our internal group. If we believe that there is -- you know, it relates to the drug, then we report it.

DR. RIDDELL: But you don't have any specific trigger points, or it is just a feel for the instance?

DR. CAMPBELL: There are specific trigger points. My two colleagues, who would know that, you know, had a flight back to Portland this afternoon. But I know there are trigger points. I don't know particularly what they are. Larry might. Do you know? But I know a number of the -- you know, especially the anaphylaxis incidents and so forth, you know, that we had ProHeart. We reported it and, you know, rolled into Fort Dodge's data and then into the FDA data. Is that your question? We didn't have any deaths, so obviously we didn't report any.

DR. RIDDELL: Okay. Thank you. One other question to Dr. Cobb. You were pretty explicit in saying as far as the thermal stability of the microsphere was 40 degrees centigrade. Is there any indication that either a local or a systemic pyrexia would affect that once it is in the animal?

The stability of the matrix?

DR. COBB: We have no information on that. We do know that under laboratory conditions if that product is heated to 40 degrees it will agglomerate and clump because there is a change in the form of that glyceryl tristearate.

DR. RIDDELL: And if that were in the animal, how might that -- I know this is speculation. How might that impact the pharmacokinetics or the dispersal of that product? Or is it in an animal system, in a live system, not likely to occur?

DR. COBB: I really cannot speculate how likely those sorts of temperatures would be consistently reached within an animal. What I can tell you is that the release profile of moxidectin is very dependent on the spherical shape and the diameter of those microspheres. So if those microspheres become clumped, the expectation would be that there would be a slower-than-expected release of moxidectin because the surface area for release becomes smaller because of the agglomeration. That would be my speculation.

DR. RIDDELL: The logical conclusion would be that would not lead to toxicity but might lead to ineffectiveness. Thank you.

DR. CRAIGMILL: As chair I have one last question, and then I am going to ask Joanne --- if she will put up a slide because I would like to use it. We do have some sort of discrepancies in data. Dr. Hustead presented a slide which appeared on page five of our handout showing the total adverse events reported by year for three different products by year from 2001 to 2003, and I would like to just have some comments on these data because they show a dramatic increase in the number of reports for other heartworm meds. I would like to address this as a question related to under-reporting and whether or not the simple awareness that there had been some problems or things reported with relation to ProHeart has also caused an increase in adverse event reporting. I will particularly ask FDA personnel to plesae comment on this slide and what they think.

(Slide.)

Are these data correct that in fact ivermectin and pyrantel, the number of adverse reports has dramatically risen as well as for milbemycin?

DR. BROWN: I would like to go ahead and address some of those if I may. As I think you may remember from Dr. Post's slide, we do have a lot of reports sent in across the class of the macrocyclic lactones. Now you will

see that there is a big change in the number of reports for both milbemycin and the ivermectin pyrantel products.

One of the things that affected that was interpretation of the regulations by various sponsors as to which reports they should be sending in or not. When new interpretations were made clear to those other sponsors, they then sent in the reports that they had not so previously sent into us, and almost all of those -- I would say all of those were reports of ineffectiveness. Not just for heartworm disease, but also for roundworms and hookworms. So that is something. They sent a huge a number of those in all at once, and they went back to before the year 2000 and it took quite a while to process them all in of course.

That is a second part of that, which is that reports initially are triaged when they come in to the Center for Veterinary Medicine. We have drugs that have been on the market for years and years and years, and we feel that we have seen the types of adverse reactions, serious adverse events that occur with them and ideally have addressed those concerns already. For the newly-marketed drugs, we give those our priority. We evaluate those as quickly as possible when they are received, usually within a week, sometimes within a month.

But when we started to see back in 2003 that there were possibly situations that there could be concerns of ineffectiveness or other problems across this class of heartworm preventives, we went back and reviewed the reports that were waiting for their turn. And we pulled all the reports for all the heartworm preventives and reviewed all of them so that we could effectively make these comparisons, and that can show you these increases. Now Mary Bartholomew also has a comment to make.

DR. BARTHOLOMEW: I think it is perhaps fairer and more germane to the safety discussion going on right now to see the next slide, to take a look at the next one, then the effect of the increased reporting. Okay. That's the one. Then some of the effect of the increased reporting has been removed, and if you will take a look in the year 2003 then you get a sense of for two drugs that have approximately the same percent of market share what the adverse events are minus the ineffectiveness reports.

DR. BROWN: And I would like to add also to that that of course these are all the adverse events that come in, not necessarily the serious events that come in. So perhaps you might see a great deal of the regular kind of vomiting or diarrhea sort of reports coming in for those other products as opposed to the more serious events we have

been discussing for ProHeart 6.

DR. CRAIGMILL: So basically what you are saying is that these data are not really correct?

DR. BROWN: Well, I wouldn't say that they are not correct, but they are not correct when you think of the severity of reports that are coming in and considering the time period for which those reports are being submitted. In other words, you are seeing a jump in reports for these other heartworm products that have been on the market for years and years. Suddenly the are submitted within a certain year, and evaluated and entered into our system within a certain year. So from that standpoint they are correct, but looking from the point that they are going back for a number of years, just reported in one year, and that they are not necessarily serious events but more likely to be the more run-of-the-mill things like vomiting or diarrhea then I think that puts it in perspective.

DR. CRAIGMILL: Okay. So many of those reports of adverse effects for 2003 for ivermectin pyrantel, and milbemycin are actually from past years?

DR. BROWN: That's correct. That's correct. They may have not been submitted because of a difference in the reporting regulations, or they may have been submitted but have been waiting for their turn in evaluation. Whereas

the more recently marketed heartworm preventives are evaluated completely within a week or a month. The second set of the next most recently marketed would be getting the next priority, and under normal circumstances these would be getting the lowest priority. If you remember, we have seven people working part time to do these effects, and we get more than 25,000 reports a year. We have to usually let some of these reports wait their turn if we feel they have been out long enough and we have seen enough of them so that we know we are not getting any new information from them. But then in this circumstance when our concerns became evident across the class, we felt we should look at everything and get everything into the system.

DR. CRAIGMILL: Will you be looking to see in terms of adverse events, serious adverse events, what fraction of those that are of that influx that came in 2003 are actually from 2003 cases? In other words, are you going to separate out the past history from the current situation to see whether or not there has been an increase in reporting?

DR. BROWN: Yes. In our internal system, in our internal database we do that. We do that by the correspondence date, and we can also search then on the actual episode date. So we can look to see how many of

those occurred within a certain time period. And I think as you saw from our slides, we then looked at all of those classes and the adverse events for them during specific -- the past three marketing years, which were the first three years that ProHeart 6 has been out, and I think there you could see really quite clearly that we simply don't have the number of serious events for those drugs that we do for ProHeart 6.

DR. CRAIGMILL: And you feel those data are complete?

DR. BROWN: Yes. I do.

DR. CRAIGMILL: Okay. Could I ask for Fort Dodge?

DR. HUSTEAD: Sure. We believe the data is absolutely accurate. We obtained it from the CVM, so we assume the data is accurate as presented. We don't have any information as to when the events in 2003 for the other products actually occurred, because that is not part of the data set that we asked for. As to seriousness, there is no information in this data to know whether the events are serious or not. So that conclusion cannot be made from the data presented. They are just numbers of adverse events. These are the lack of efficacy events removed, so these are the events regarding safety.

DR. MEALEY: I have a comment on potentially what else may contribute to maybe an increase in reporting for all of these macrocyclic lactones. The discovery of a genetic mutation for ivermectin and macrocyclic lactone activity occurred and was published in 2001 and then picked up by, you know, AKC Gazette, and Dog World and Dog Fancy and then distributed by email all around, you know, the world about some of this stuff. I get emails and I was really getting a lot of emails during those times as well about any kind of -- any macrocyclic lactone in any breed and any potential toxicity. I was getting those at this time. So I think that that discovery generated interest to some extent in these compounds again, and so perhaps -- and I have no data, but I am just saying perhaps -- I am speculating -- that may have contributed as well to maybe an increase in the number of adverse event reports.

DR. CRAIGMILL: Any further questions from any member of the committee?

DR. TREPANIER: I have another question for Dr. Glickman then, because I really think the Banfield study is -- I think that data is so important, but I think that is also important to look at it from as many different ways as possible, and I think -- I know you have done multivariant analysis, but I think it would be important to look at all

the animals that got moxidectin and do actually a case control -- a matched case control comparison, same age, same health status, a very important one, perhaps same breed. Because the patients that got monthly heartworm may well be sicker, older, have other reasons to have anaphylaxis or vomiting or diarrhea, and it really clouds the issue. It seems like it is such a huge database. You can rely on the healthy dog studies that were done pre-approval because they are such a small number and it is clearly a relatively uncommon set of reactions. So is there a way to look at that data? It seems like that would be very important.

DR. GLICKMAN: There are many ways to look at the data, and there are lot of things that are attempting to do and should be done. In a sense doing subpopulations at risk, is there a unique group of animals either by their age, their medical history, or whatever, that would be more likely to react to one of the monthly heartworm medications than to ProHeart and vice versa. I agree with you. You know, you get a database this size, this rich in information, there are so many things you can do, and you have indicated another approach to doing what we tried to do by adjustment. I don't know that one way is better than the other. Certainly the two methods should give consistent findings. But the tendency is when you have a database this

large and have it over so many years, rather than doing the retrospective approach like you are talking, and matching and going back in time, it is to do this forward analysis. The big advantage of doing it the way we did is we can come up with an absolute risk, and incidence rate which gives you an absolute risk. What is the likelihood that if an animal got something they will have such-and-such reaction. Where if we do it the way that you suggest we lose that, but we can compare relative differences.

DR. TREPANIER: But can we say from that data that the groups that got moxidectin were same as the groups that didn't as far as -- you said you looked at that demographically, but it is not supposed to be used in debilitated animals, yet plenty of clinically ill animals get monthly heartworm preventative.

DR. GLICKMAN: I think the better way to answer that question is not for me as evaluating the data, but from Dr. Campbell in terms of what the protocols are for selecting dogs to receive, you know, oral versus injectable heartworm. You may want to comment on that. In other words, why would one animal get one product? Is it really up to the owner for the most part?

DR. CAMPBELL: Well, you know, it is up to the owner, but it is also up to the doctor. We believe that

it is the doctor's ethical responsibility to make a recommendation. Our doctors really believe that the best efficacy of all of the heartworm medications is ProHeart because we know that they got it, and so, you know, I don't want to, you know, embarrass anybody the room by asking who has oral heartworm medications in their drawer, but I will admit that I do, are overdue for my own dogs. So the reality is our doctors primarily when it was available prescribed ProHeart, not the orals, because it is a lot better product, and it is really, really safe. You know, so does that answer your question? Not really. Okay. So what was the rest of the question?

DR. GLICKMAN: But as far as I know from what I know that Banfield practices and what I saw in the database, there are no deliberate inspection criteria that a sick animal would get one product versus a well animal would get another. The preferential treatment is for ProHeart.

DR. CAMPBELL: Oh, absolutely not. If there was a sick patient we wouldn't prescribe either one, you know, and what we look at are what we believe are the barriers to care. You know, the things that stop people from coming in and getting care. So, you know, over 60 percent of our patients don't have to pay for office calls to come in because we want them to come in if they are ill.

So, you know, the doctor at that time will see on the computer what has been prescribed for that patient, and if they are on an oral medication they are going to say don't. You know, don't give that until Buffy gets well. So, you know, I don't think we are prescribing either of them, you know, if they are ill. Now the thing is if you give ProHeart and the pet gets ill four month later, you know, they have already in essence had it, you know, and so I suppose there is more of a chance that an ill dog is going to get -- has already got ProHeart than it is they would get an oral medication I think. Isn't that right, Larry?

DR. GLICKMAN: I think so. So I think the bias would be the other way.

**Deliberation on Question One**

DR. CRAIGMILL: If there are no further questions from the committee, we will go to deliberations and do a tally in response to these questions that were presented to the Advisory Committee by FDA. What I will do is I will basically do a tally and go around and ask individuals. We will do one question at a time. We will start with the first question, which is "Based on the presentations and information provided is ProHeart 6 safe for use in dogs?" We have been asked to provide a yes or a no answer. Personally as a toxicologist I don't like the

word "safe". I say this every meeting. I want to say acceptable risk, so that is the way I am going to answer it. You can go ahead and -- go ahead with a yes or no, but then please fill in afterwards qualifications, you know, whatever. So what I will do is I will go to the members and then go down the list, and Dr. Aref, Susanne.

DR. AREF: I have a hard time saying yes or no because I don't think we have seen enough good numbers. I think CVM or FDA has provided the sort of most -- have included a lot of numbers that might be sort of on the edge. I think that FDAH has excluded some numbers that they shouldn't have. I had a hard time especially with the last table we looked at where it looks like you have exactly the same adverse event for the two top products in the table. So I would say at this point I would say no, but maybe with further testing. I just don't think I can give an answer based on the knowledge we have.

DR. CRAIGMILL: Thank you. Corrie, Dr. Brown.

DR. C. BROWN: Very difficult to answer that question. I thought the Banfield data was excellent, and based on that it appears that ProHeart 6 is safe for dogs. The CVM reporting would indicate otherwise, but I had some problems with that data in that much of it seems

inadequately documented with respect to cause of death, and the manner of reporting seemed to me somewhat haphazard and a little subjective. So I would like to see that data put into a more rigorous format before deciding.

DR. CRAIGMILL: I'm supposed to press you for an answer.

DR. C. BROWN: I would be inclined to fall on the side of, yes, it's safe.

DR. CRAIGMILL: Thank you. Gregory Jaffe.

MR. JAFFE: I also have the difficulty in using the word safe because I think safety is not absolutely and I think in the end. But I guess I would answer the question if this sort of -- if the question is asking should this drug be back on the market tomorrow or not I would have to say no. I think at this point we still need some additional data to insure that it is safe for drug use. I think the data that FDA presented does put that into question, and so it seems to me should err on the side of getting more data before the drug goes back into use. I had difficulty understanding the different data sets because I think they didn't try to be comparative but tried to actually confuse. It would have been nice if FDA had been able to put some rates down there for rates. It would have been nice to better understand --- reports. Both groups

were using different numbers of describing them differently so that made it difficult. But it seemed to me there were enough adverse incident reports that FDA identified to question the use of this, and I think the voluntary recall should continue for the time being.

DR. CRAIGMILL: Thank you. Dr. Mealey.

DR. MEALEY: I don't envy the FDA for making this kind of a difficult decision, and like I said before I think it is difficult to determine if was the drug moxidectin that was actually the cause of some of these things or if it was the carrier or vehicle. I think the data for the liver, for some of the immune-mediated diseases, for the neurologic diseases, it is very difficult to say one way or the other because they were conflicting. They had data from the Fort Dodge that is very different from the data from the FDA. But the anaphylaxis in both the FDA and the materials provided by Banfield shows that anaphylaxis is greater with ProHeart than it is with any of the other heartworm preventives, and because, one, there are other --- there are alternative agents out there. Yes, ProHeart is comparable to vaccines, but I don't -- I think that is comparing apples and oranges. So I would compare ProHeart with the other heartworm preventives out there and at this point say that compared to those -- well, obviously

none of them are 100 percent safe, but I would like to maybe see a little bit more information there. And the fact that ProHeart is going to be administered more often than vaccines makes me err on the side of saying no, that it is not safe.

DR. CRAIGMILL: Thank you. Let's see. Dr. John McGlone.

DR. McGLONE: Well, thank you, everybody, for your presentations. I know it took a lot of time to prepare. I was trying to figure out what the facts are in this situation, and that is a difficult set to identify, and I came up with three facts.

One is that mostly from the written material that the product, as with probably almost every product, is toxic at very high levels. Not at the levels that are sold commercially of course. So that's one fact.

Secondly, there seems to be multiple factors that interact with adverse drug reactions with ProHeart 6. Most notably the age of the animal and whether it has been vaccinated or not, and these interactions might help explain some of the variability that is observed maybe.

The third fact, which is the fuzziest fact of all -- they get fuzzier as you go down the list. The third fact is that finding in the field are highly variable, and

that is not much of a fact is it, because it doesn't say one way or the other what happened. But there are some -- well, my characterization is that most of the reports from the field are largely positive on its effects, but there are some significant negative findings that cannot be ignored. It suggests a need for research to understand what those interacting variables are and how they can be managed through label change or training.

And the fourth fact -- I said there was only three -- is that the levels of adverse reactions are low. They are low in the general population and they are low in the subject animals here. So the risk it seems to me doing -- for some other purposes we use a qualitative risk assessment, and that is what I am still thinking about from our last meeting. It seems that the risk moves from very, very small to very small when you use this product, particularly when you use it in combination with certain other products and under certain circumstances. So moving a risk from a very low number to a low number doesn't clarify whether it is safe or not, because some people would not accept -- would accept zero risks for their pets for example, and they wouldn't like to move the risk from very, very small to very small. Other people might be willing to take that risk in favor of some benefits.

I don’t think that there is enough information to do a proper risk benefit analysis for this product at this moment. I think there is too much variation in reports from the field. That has to be understood so that you can manage the risk a little better. So it depends on where you draw the line on safe, whether you draw it at, you know, whether the risk is moderate, or small, or very small, or very, very small. That is why the committee is having a problem. So I would say in the interest of the people who are highly motivated to not have their animals suffer that moving from very, very small to very small is still a risk, in which case I would have to say it is not safe at that level. Under other circumstances it might be an acceptable risk, but not in the current situation. Thank you.

DR. CRAIGMILL: Are you a lawyer, John?

(Laughter.)

DR. CRAIGMILL: Should I mark that as sort of a no at this point? I did. Thank you. Dr. Nelson. Oh, excuse me. I haven’t finished with the committee. I haven’t even figured -- Dr. Nolan, Lisa.

DR. NOLAN: I thought it was a very valuable session. I appreciated everybody’s input. I was very touched by the folks who had lost their pets or family

members as they referred to them. They reminded us how high the stakes are I think in this drug. For me, I found the evaluation of the Banfield data to be quit compelling in support of the use of ProHeart, but like Dr. McGlone and others before him, I am impressed. I feel like it is relatively safe, but I would qualify that.

DR. CRAIGMILL: Thank you. Dr. Papich. That was a yes, yes? I got a yes out of that, a qualified yes. All of these answers are qualified. We are not going to have any straight ones.

DR. PAPICH: Well, we know that all drugs can produce some adverse effects, but when I look at adverse effects produced by drugs I differentiate between drugs that are used to treat a disease and drugs that are used as a prevention in healthy animals. Drugs that are used to treat a disease I think we do accept certain risks and we have a higher threshold for those risks because we realize the stakes that are present. But when a drug is used to prevent a disease and it is given to an otherwise healthy animal, I think the bar is raised a bit and I think we do have to have a higher standard. I also consider the nature of those adverse effects. If it was something minor like loss of hair at an injection site or something that is -- that an animal can recover from, that perhaps is acceptable. When

it is the death of an animal it is not, and I was compelled as was Dr. Nolan here by the visitors that we had today and some of their testimony.

I think that not only do we need a higher standard in considering and evaluating some of these products, but as a veterinarian I am a little bit ashamed of the veterinary profession in the way they have reacted as was cited today here. I think veterinarians could have handled this a lot better. But considering all of the data available, I am inclined to say no to this question at this time, but I leave the door open that we still have a lot to learn. The Banfield data, although very good, I am concerned whether or not we are relying too heavily on the Banfield data in comparison with other potential sources of data. We don't know at this point, at least I'm not sure, whether these reactions that are possibly caused by the drug, caused by the vehicle, caused by some other characteristic of the formulations. So there is a lot I think that we have left to learn about this, and it is not a dead issue perhaps. But maybe as we gather more data and learn more about this we will be able to understand the nature of this, of these reactions.

DR. CRAIGMILL: Okay. We move now to consultants. Dr. Bennett.

DR. BENNETT: Okay. I think it is really a tough call as well, and my question is for the second question. If we answer the first question and say is it safe, does that mean we're not going to address the second question?

DR. CRAIGMILL: No. In my opinion we are going to address it no matter what.

DR. BENNETT: Okay. Because I am sort of qualifying as everybody else, and I'm a qualified yes. I think clearly the cases, the reports are dramatic and worrisome, and my biggest issue again, because I live off of MedWatch databases and I look at these adverse events spontaneous reporting system, and I put those at the level of -- I go level one through five. I put those at level five in evidence because of the quality of the adverse event reports that come into the stars of MedWatch database, and I know you have a difficulty with that, too. The Banfield database had a little bit -- had some value to me because of the numerator/denominator issue, which is what I worry about mostly, and I wish we had four more Banfield-like databases so I could feel more comfortable that that was replicable around the country. I am concerned that there is no other Banfield-like database out there. Maybe there is or isn't. I'm not sure about that. If there were I would love to see

it, and otherwise I would say if I could see three more like that I would feel much more comfortable with my qualified yes. But yes is the way I put it.

DR. CRAIGMILL: Thank you. Dr. Luster.

DR. LUSTER: I thought the cases today by all the presenters including the Fort Dodge people and the public and the FDA were very strong. I just wish the data sets that they had or the way they could collect the data was a little bit stronger and could make our answer a little bit easier to come to grips with. But I think that from what I could tell is that some of the endpoints that they are looking at, some of the clinical manifestations, appear to look like there was an increase with ProHeart 6. So I have to vote no at this point, although -- and this was especially related to the anaphylaxis and --- type responses, although the incidents were really small, but they seemed to be prevalent there. Particularly in the sense that there are other drug alternatives other than ProHeart 6. Saying that, and probably what everybody else is thinking as well, but there is really a need here to conduct some sort of risk benefit analysis, particularly considering that there is an apparent high level of noncompliance with the tablets. But that data wasn't presented. It was just a general percent. I have no idea

what the noncompliance would be with ProHeart 6. I mean, I know if you go in and tell your vet will give it to you, but not everybody is going to go in and get a shot all the time. So anyways, I am saying at this point it is a no.

DR. CRAIGMILL: Okay. Dr. Groseclose.

DR. GROSECLOSE: Well, I appreciated both the testimony and the presentations by the various presenters and would agree that the quality of the data is really lacking to make any sort of decision. My vote is a qualified no mainly because I think there are data available. I think the clinical trial data that was presented suggests that there is really an adequate sample size to really answer most of the questions that are presented, and the Banfield piece is really a -- it appears to be sort of a retrospective look at a large population but is suggestive of low risk, but is not -- it doesn't have the quality of evidence that a clinical trial would have. I think the post-marketing surveillance by both groups, both the FDA and Fort Dodge, really are inadequate to address the question as well. I mean, they are basically numerated data and it is hard to say what the source of some reports were. We just didn't have that information. So a qualified no at this point.

DR. CRAIGMILL: Dr. Nelson.

DR. NELSON: I, too, want to make a comment that with the pet owners that were here we all sympathize with them. We went into this business because our pets are important to us, too, and when it is your pet it doesn't matter what the statistics are. If it is your pet, it is 100 percent.

Also the American Heartworm Society has not taken a position on this, but being a member of the society I am privy to lots of information from around the country, have veterinarians call us about the -- or email us about this particular product. And over a year ago when questions were coming up, or two years ago, you know, I spent a fair amount of time answering questions and also reviewing databases like on VIN and see what the comments are, calling colleagues, calling professors, universities, and trying to in my own mind find what kind of incidence is out there. And the more we looked, the more I looked, especially when the veterinary professionals are saying it was nine to one no problems, and there was --- a problem.

There was mention about this being a preventative drug, and we need to hold it to a higher standard, and I will agree to that point partially. When you look at the number of heartworm cases that we see every year, when you look at the statistics on compliance and

those people who purchase monthly preventatives and the 60 to 75 percent of the doses being given and the rest sitting in the draw. The number of cases that are going around out there, you also have to look at the number of animals that are getting heartworms and suffering and dying because of lack of proper preventative administration.

One of the things this product did was to address that issue. It also helped us address it other ways. My own particular practice, you know, when we started giving the injection we started sending reminders of the injection. We also started sending reminders for all the preventatives. But still we would find just the compliance rate was not there with the monthly pill.

Then also, you know, talking about making the decision based on the information provided today and provided in the reports, and when I review the clinical cases that are supposedly representative of the situation, I just see too many other possibilities for causes. While there is no 100 percent safe drug and no 100 percent effective drug, I would have to say a qualified yes.

DR. CRAIGMILL: Dr. Peterson.

DR. PETERSON: I have the advantage of having heard most of the other folks give their opinions so I can better formulate mine I guess. I think it is important to

keep in mind that the system that CVM has in place is a passive surveillance system, and I think it did its job from the standpoint that a passive surveillance system really does no more than raise the index of suspicion, which I think it did in this case. I think the data that speaks most appropriately to whether or not we have a safe situation, and I would also comment I don't like the word safe, but I have a little bit different perspective on that. I think the wrong question is being asked. I think people are making decisions based on at some level, an unknown level of what is safe and what isn't safe. I think a more appropriate question quite frankly is "Relative to the other products out here how does this product compare?" I think that is a little bit different question, but I think it is the more appropriate question. I know it is not being asked, so I will answer the one being asked. But I just want to make that for the record, that comment.

There were comments made relative to the increase in anaphylaxis as being a contributor to some people's decision. I think there is given the real world data and given how this preventive is administered, I think strongly biases any difference you would see and any increase in terms of anaphylactic reaction. As practicing veterinarians I think we all know the potential to see a

more immediate anaphylactic reaction I think was well described, and you tend to see that when you administer a product that is administered by injection as opposed to something that is given orally and you don't even know in fact when it is given, whether or not there was an association with their oral medication. It is more easy to determine a point in time association with an injectable. I think that tends to bias people's perspective on what is cause and relation here.

My feeling is that the Banfield data is really real world data, and I know as an epidemiologist I really don't know any other way to find out whether anything is at increased risk for causing problems, particularly relative to other medications that are designed to do the same thing other than a real world situation. I will grant you the data is not perfect, but I would also point out that that data, at least in the field of veterinary medicine, is very rare to have available to us. I think everyone here is familiar around the table with the veterinary literature, both in research and the clinical literature in terms of, you know, case reports of literally 60 to 100 cases, and that is generally pretty good. What we are dealing with here is hundreds of thousands of real world cases. My feeling is that that data very strongly demonstrated that

there is a lack of safety, however you want to define it, across all three drugs that were tested. I think it also demonstrated that there really wasn't much difference among those three drugs, particularly when you take into affect what may be contributing to the use of an injectable versus -- in terms of the reporting system, particular with reference to anaphylaxis relative to the oral medication.

So I really don't have any problems in making the decision that the answer to this question is yes, because I think the bigger question that needs to be answered is what is the relative safety of all of these types of medications. And I would tell you I have had some experience on the human side sitting on the Advisory Committee for Immunization Practices. I have seen the pictures of the babies who have died because they were attributed to deaths attributed to immunization for human vaccines, and while these are possible, I think what you have to do is you have to do some type of a risk benefit. Make a decision. I would propose to you also that I don't think that we are every going to have in the next one, two, even three years, definitive answers that will satisfy everyone to the question of whether or not something was safe. So my answer, and I don't really have any reservations based on the data I have seen, my answer to the

question is yes.

DR. CRAIGMILL: Thank you. Dr. Riddell, Gatz.

DR. RIDDELL: Well, I would like to thank all the parties involved for the material they presented to us, the presentations they made today, and for the people who came and gave the personal stories. My congratulations for having the strength to do that. When I try to evaluate decisions that I have been involved with that deal with topics like this, in the end it comes back to doing everything you can in a science-based mode. And granted science is not perfect and that is always going to be a difficult thing with something that is very subjective like this. I understand some of the comments about holding preventatives to a higher power, but yet we still have to remember that every pharmaceutical agent that we put in an animal has potential to have very powerful effects, whether it is very new and cutting edge or whether it is old. So those are concerns I think we -- there is not going to be -- obviously there is not a perfect adverse event reporting system. Otherwise we wouldn't be sitting here talking about this. But I think there's several strides to be made in that direction.

Looking at the same thing for the risk

benefit analysis, but the risk to a patient whose owners do not do better than the average for compliance in heartworm-infested areas is pretty severe. So when I look at that, look at all the possibilities, and look at what seems to be -- not being an epidemiologist, but judged by other people's evaluations to be the best data and the best science that is out there, that being the Banfield data set, I would have to say a qualified yes.

DR. CRAIGMILL: Thank you. Dr. Trepanier, Lauren.

DR. TREPANIER: Well, I also think the Banfield data is important. I think one piece that is missing from that data is a 30-day phone call to these clients to confirm that there were no adverse events in that time period, and we don't have that. We have a three-day phone call and then really relying on the owners to come back to them if there is a problem. And I do believe there is a lot of power in that data set. It does appear that these reactions are rare. It does seem from what the FDA presented that there does seem to be a higher signal in the patients that got ProHeart, and it may be because of the way it is administered and the way it is monitored. But these reactions when they occur can be catastrophic, and I also agree that there is a higher bar for a drug that is used in

a healthy, young animal where there's no other problems and then death is a potential side effect.

So I would have to say no since the burden of proof is on the company to prove that it is safe to a reasonable level, and I think when you look at relative risk you really need to put this drug in the context of how much extra protection is it going to give versus oral medications, which do appear to be safer at least based on the FDA data, and I think that is something that needs to be looked at. If this drug really truly does save more lives from heartworm then there may be a risk that can be accepted. So I do think that a more rigorous risk benefit analysis is really important.

DR. CRAIGMILL: Thank you very much. Am I supposed to vote, Steve? Not vote; give my assessment to this answer.

DR. SUNDLOF: (Nodding head.)

DR. CRAIGMILL: First of all, Last night about 8:30 Aleta came with a -- yes, Dr. Sams is not voting at this time. Last night about 8:30 Aleta handed out a package, double-sided copy of public comments. For the person who wrote in here that he thought that his comments would not be read, they were but at least one member. I went through all of these, and I am sure many of the others

did, and there are some very touching personal accounts of having lost pets. Having lost pets of my own I can relate to them very dramatically.

The drug in question here has basically been tested thoroughly according to all the FDA requirements, and the FDA accepted it on the basis of all those requirements on the studies that are normally done by any new animal drug to satisfy safety, effectiveness -- that's the most important things. That said, the number of case reports, there is no question that there have been a large number of adverse reaction reports on this particular product that have come in. Why do we have such a discrepancy between the FDA opinion of this and what is going on with the company's opinion of this? I don't know how to resolve that issue. I find it difficult to juggle those, and I am not sure whether even if we locked them in a room for a couple of days they would come to the same conclusion with the same data -- although it is an interesting idea.

(Laughter.)

DR. CRAIGMILL: When I review these data and again as a toxicologist I look at things in terms of acceptable risks, safety being an acceptable risk. For some people it is unacceptable. A risk is basically a probability of an adverse reaction occurring or an adverse

event. For the people whose dogs were affected that risk was one, and they have suffered the consequences and it has been awful. For thousands of other people who have used the compound, have had it, that risk was zero. It is acceptably safe to use this drug? I would give a qualified yes to that in my opinion, but I also will have some further comments when I get down to the section on safety concerns. Basically everybody here has said we need more data. How are we going to get more data if we don't have the drug being used? We are not. If this a drug where we can state there are acceptable risks and possibilities for gathering more information to further define those risks more effectively, that is why I am going to give it a qualified yes at this point. I love being last.

**Deliberation on Question Two**

At this point I would now like to -- again we will go through the ranks here and ask the following. "If there are remaining safety concerns with ProHeart 6, what additional avenues of research could be explored to mitigate and/or prevent the adverse events?" In other words, what do we need to do? And at this time Dr. Aref has been able to listen to us and formulate her answer. So one more round.

DR. AREF: I am not sure that -- I mean, I get worried about the multiple logistic model sometimes when

-- I don't know that all of the aggressors would be completely not correlated. I mean was the modeling investigated for that? So, I'm sorry, this should have been a question before. I mean, possibly somehow all these different data gatherings ought to be somehow put together to make for -- well, I don't know. The data is so confusing and not adding up somehow. Further research with further clinical trials maybe. I don't know. But that seems to be the only option if the drug is going to be accepted at some point, or since we are only doing qualified yeses and nos.

DR. CRAIGMILL: Thank you. Dr. Brown.

DR. C. BROWN: Well, I would like to suggest some things that can be done with the existing data, and that would be to take a closer look at the cases that have occurred and to really dissect out the other confounding factors. In particular administration of other vaccines at the time. What brand of vaccines were they, what was the -- how many times had the ProHeart 6 prior to that. So that would be from an epidemiologic sense.

But then I would also like to see a better follow-up with the animals that die and a correlation of the necropsy and histopathologic findings with the clinical disease and also the time frame post-administration. Does it all fit together with a toxicologic pattern, or are some

of these deaths due to something else and they are being report as adverse drug events, but really they are spurious incidents?

Then the third thing would involve some proactive work on the part of Fort Dodge Animal Health, and that would be the moxidectin administration, the ProHeart 6 administration at the same time as creating a febrile illness in a dog to see what those levels are. You mentioned that with a clumping at 40 degrees there would likely be a decrease in blood levels, but do we really know that? Thank you.

DR. CRAIGMILL: Thank you. Gregory Jaffe.

MR. JAFFE: Being I guess the one non-veterinarian medicine doctor here on the panel, it is hard for me to talk about the avenues of research that might be explored. But I think I would say that one of the things that might be done here is the Banfield data has been reviewed by Dr. Glickman, but it hasn't been reviewed by FDA I don't think and they haven't had a consultant analyze it. Since there is a lot of data there, it might have somebody else do it, a different analysis of that data. Especially taking in some of the comments that other panel members have said today, might be able to come up with confirming that information or providing additional data about the drug. So

I think that would be a useful thing to do. I think if you were to continuing using it there might be additional conditions that might be put on it if the agency decided to do that. Maybe it shouldn't be given with a vaccine at the time to get rid of some of these possibilities of something else happening. Maybe there should be a follow-up for the veterinarians to fill out with the patients afterwards to bring in data to the agency in a certain percentage of the number of vaccine -- the number of shots that are given so that we have some affirmative follow-up. So I think there are ways that if one is to continue giving the drug that they could get additional data at the same time and also get rid of some of the variables that seem to skew what we have in terms of the data now. But I think also having some of the parties look at each other's data some more might help get some additional information.

DR. CRAIGMILL: Thank you. Dr. Mealey.

DR. MEALEY: Not being an immunologist I am not sure that I can help anymore here except for maybe some more experimental investigation into the potential causes for anaphylaxis. Not specifically with moxidectin, but maybe with the vehicle. I would love to see another independent data, group of data. I have some concerns that there may be a bit of a conflict of interest with the

Banfield data. Maybe collective information from veterinary institutions, from the colleges of veterinary medicine collectively might give similar quantity of data as the Banfield data. And I would like to see more data on the efficacy and compliance of ProHeart versus some of the monthly. That has been one of the criticisms, that there is not good compliance with the monthly heartworm preventives, and I guess I would like to see data that it is easier for people to come in to a veterinary hospital twice and get an injection than administer doses of heartworm medication at home.

DR. CRAIGMILL: Thank you. Dr. McGlone.

DR. McGLONE: Well, as I might have said, I don't think there is really enough data to do a risk benefit analysis. But it seems to me that Fort Dodge Animal Health is highly motivated to collect such information, and the nature of that is really you need three kinds of studies. You need some basic studies on mechanisms. You need a large-scale clinical field trial, because I don't believe the 280 dog study was large enough to show even a small incidence of some of the problems that have been seen in the field. Maybe you won't see any even if you have 2,000 dogs, but a larger study would have a greater chance in such a thing. Then I think you need a prospective epidemiology

study. You need to start from scratch and agree on what you are going to collect and collect relevant information for a long enough period that you have confidence in the data. Perhaps from more than one Banfield-type organization.

I do think that there is an inherent problem in veterinary medicine. I can say that because I am not a veterinarian I guess. In that a lot of veterinarians including my veterinarian that takes care of my dogs sell the drugs. And when I go to the physician, he doesn't sell the drugs. In fact, he gives them to me for free, and then I go to the drugstore and buy what I need. So the physician doesn't have the kind of conflict of interest that veterinarians have. So that is kind of problem, because the members of this committee are asked to declare and live up to these positions, but the people in the field don't have to hold to the same standard. So basically we have a general problem with getting quality information in just a retrospective sort of way. So if you start from the beginning and set it up where that is not an issue, then you will get a larger quantity of data that is of higher quality.

Then when you have that, I think a change of label if appropriate -- it might not be appropriate -- and training of people in how the product is used and delivered

would be appropriate. I think that when you have the label change and the training organized, then you can do the risk benefit analysis and you will probably see that it's a wonderful product from the point of view of the company. Thanks.

DR. CRAIGMILL: Thank you. Dr. Nolan.

DR. NOLAN: Well, it seems to me this drug addresses a real concern in heartworm prevention and with other -- prevention of other disease, and that is compliance. If it is used it can really lead it looks to me to a decrease in a terrible disease. It would seem to me that risk benefits analysis would be dead on and very helpful in evaluating this drug. Unfortunately I am not a statistician, so I can't say what that involves. I would also wonder if it is possible to do some kind of follow-up study, a 30-day callback in the future to see if we can do some long-term stuff on it.

DR. CRAIGMILL: Thank you very much. Dr. Papich.

DR. PAPICH: We have raised a lot more questions than we have answered, and I think there is lots of room for some other investigations. I agree with the comment that somebody brought up earlier that if this drug is not available anymore there is not an ability to collect

more data. However, there is data for which we have records. If it is possible, it would be very helpful to try to mine data that -- other than the Banfield data that would perhaps be of some consistency that we could use to compare, and I think that would be helpful. Whether that is available or not, I'm not sure.

In the presentation one of the things that I found one of the most interesting was the relationship between the onset of some of the adverse effects that have been reported and what seemed to coincide with what would be a peak drug concentration after administration. That is one of the reasons I had asked some of the earlier questions about the kinetics and the release of the drug. That seems to me to be a relationship that we shouldn't ignore and could be explored further, perhaps looking at a larger group of dogs and looking at variability and release of the drug after an injection and looking at other conditions that may affect the release in a group of dogs. Pharmacokinetically it might be helpful.

Of the reactions that have been seen, I think there are some of them that appeared in the record such as malignancies that are I think perhaps red herrings. I don't think that this drug probably leads to malignancies, and it is possible that some of the elevations in liver enzymes

didn’t have much to do with the drug. But the reactions that appeared immunologic in nature, those are -- and those were the largest group it appeared. Those are ones that I would hope that someone with better immunologic background than I do could think of some ways to explore that.

Also in dogs that have had reactions, if it would be possible it would be fascinating to explore potential genetic relationships among the dogs that have had similar reactions. We have experts on our panel who are better experts in pharmaco-genomics than I certainly am, but I think they would agree that pharmaco-genomics is in its infancy in veterinary medicine. But we do recognize that there are genetic relationships among the dogs that have certain types of reactions, and if that could be explored among the dogs that have had reactions to this drug, that would certainly be worthwhile.

DR. CRAIGMILL: Thank you, Mark. Dr. Bennett.

DR. BENNETT: I’m thinking back on the experience I had with the immunologic side effect with --- products which we just reported, and it was very rare, but it was immunologic and it lead to some responses from the FDA that I think were very insightful. The kinds of things that the FDA did then was -- one is they elevated the

warning to a black box warning, which I know you don't have here, but a black box warning does raise a level of awareness and reporting also in the public sector to build a higher level. Second thing they mandated in the other countries besides the US where the --- was a formal prospective pharmaco-vigilant study, a large-scale one, and it was formal and it was prospective. I thought that was also a useful thing. The third thing that they mandated as well and is important is I think the vehicle is an important issue, and I think that became an issue with the other product. It raises concern about the vehicle, and I think the vehicle is something that we got some insights from you that there is some question about the vehicle. And it leads me to think for instance if the study we heard from, those people are more rigorous with the vehicle, with the product, than the other people in the community, that may be a differential reporting rate. That maybe --- reporting for the study that you commissioned, and high lights because they did say you have a formal educational effort out there. You have got a web-based educational effort out there, and the same thing with the other product is what happened. The FDA and the other countries, the other countries, the regulatory authorities, did mandate formalized and a more rigorous approach. I thought that one speaker from the

outside requested that they think about a single use file had an interesting point. It would be interesting to know if a single use file would actually get us to the point of being a little bit --- with the vehicle.

DR. CRAIGMILL: Thank you. Dr. Luster.

DR. LUSTER: I am actually an immunologist by training, and since I'm an immunologist I tend to think that most --- drug reactions are really systemic allergy in disguise. Which is very hard to, as the drug companies can tell you -- pharmaceutical companies can tell you that is hard to identify and test for, and also is a major problem for many, many pharmaceuticals. But one of the tests that are currently being used which I think is worth exploring is the simple test which I think most FDA centers use as a guideline. The test now is a --- assay of the various materials. I would think that the drug itself is technically not to be extremely allergenic, but you would think that the materials, the microspheres, have been shown some of them to act as almost like an antigen depot. So that they are really serving as a continuing expulsion of the antigen, almost like an adjuvant. So that is --- to cause more of an immune-type response if that is what is occurring. But there are ways to test for that, and one is the --- assay. One can do immuno-pathology to look for

immune deposits on tissues and things like that. So it can be done, and if that if that is the case, I mean, there is also some of the pharmaceutical companies have developed --- to remove that antigenicity, and they can do masking for example. A lot of the materials used for imaging for example in humans can tend really to be antigenic, and they put what they call masks on it so the immune system no longer recognizes it as antigenic and they can be used. So there's some potential opportunities there. That's all.

DR. CRAIGMILL: Thank you. Dr. Groseclose.

DR. GROSECLOSE: Thanks. I think there are some things that you can do with no new data. One, I would follow up on the recommendations to do a risk benefit analysis and try to model that based on what we know. I mean, I do think the issue of compliance is a real one and it would give us some better idea of the value in terms of the risks. Also I would second the recommendation for a case control study using Banfield data. I do think that would be a good use of that data set and to review -- have FDA sort of review the study design to insure that it can answer a few more questions. I also think there is a need to try to resolve the disparate data that we have. Essentially there were three case definitions for these adverse events. There is the Banfield definition, the FDA,

and then the Fort Dodge, and those data are now out and available and are generating a lot of heat. I would think it is probably worth some effort to try to resolve those.

In other words, perhaps get reviewers and more than one reviewer per case to try to use at least a common case definition and try to see what we can come up with there. Ideally you could combine data from various clinical studies that have been done and some sort of a meta analysis, but I don't think that is possible just based on what I have heard about the types of studies. I don't think that those data can likely be combined. But it might be something to think about in the future, that one design study so that you could combine those data. I think, that may take us certainly closer to perhaps me closer to a qualified yes. But the prospective issue, you know, this is apparently the only microsphere technology out there, and I think that should be evaluated through prospective studies if at all possible with the same size that is adequate to try to address that issue.

DR. CRAIGMILL: Thank you. Dr. Nelson.

DR. NELSON: Allow me to comment about the veterinarian selling the product. It doesn't have anything to do with the research, and we discussed all the other areas. We can take the data we have. But whether the

veterinarian is selling ProHeart or selling Heartguard or Interceptor, it is really not a -- you are selling one or the other. So the economic benefit is there. There has been speculation about veterinarians -- and I had to say this -- that have been going more for ProHeart because trying to eliminate the internet pharmacies. You know, I can't speak for every practice, but our particular practice in general, you know, we have always been willing to match prices. In fact, when it came up as an issue, we reviewed these major internet pharmacies, and actually it was a pretty good eye-opener for me. It allowed me to raise my prices, because I was cheaper than most of them.

(Laughter.)

DR. NELSON: And I could do it in good conscious and still be cheaper. But as the data I would like to see, we know that these class of compounds do have very potent activity against both microfilaria and immature heartworms. I would like to have a little bit better idea of actually what effect the drug has on the L4, the L5, how quick it dies. Could this be correlating to the reaction? We know when these microfilaria are acting -- microfilaria, excuse me. When these larvae, L3s, L4s, L5s, die they can produce immunological responses as we are seeing with most of these cases. So that was some data I would really,

really like to see.

DR. CRAIGMILL: Thank you very much. Dr. Peterson.

DR. PETERSON: I have to be forgiven for thinking like an epidemiologist again I guess, but typically what happens with epidemiological population-based studies is you go from something like a passive surveillance systems which identifies the potential for an excess of disease or an excess of risk or whatever, to something like a cross-sectional study which was done with the Banfield data. Based on that, typically the next step is really not necessarily a case control study, but something that is done prospectively. The problem with prospective studies, particularly in this case, is it doesn't appear there is going to be any more data in the future to collect. Secondarily the other problem with prospective studies, and it is probably even worse in veterinary medicine than it is in human medicine where this is the typical way things are done, is there aren't going to be enough -- there isn't going to be enough money to do an appropriate prospective study. There will not be enough cases collected, and Dr. Glickman pointed out that for some of these rare occurrences you would literally have to have well over half-a-million cases to identify anything that is excess risk if you are

making comparisons between groups. So at least from an epidemiological perspective I don't think there really is going to be any more data that is going to add to the ability to make a decision relative to safety.

I think one other thing, and since some of my other colleagues have kind of touched on this also, I think we need to keep in mind I think -- and this is true of human medicine as well as veterinary medicine. I think as practitioners of veterinary or human medicine I think many times we don't do a very good job for a variety of reasons of communicating risk. I think we tend to some degree to either have clients who let us make the decision, or we try to influence them for a variety of reasons, some which were given round the table. I think we are going to be faced with these same kinds of problems in the future relative to whether it is this particular drug or whether it is other drugs. Whether it is drugs you use to treat, whether it is prophylactic medications, I think it is the same issue. I think we have to be very, very careful about putting things in perspective. Otherwise we are going to be faced with these same kind of issues in the future. The same is true with human vaccines, the same is the true with veterinary vaccines, it is true with all types of prophylactic medications. There is nothing that is 100 percent, and I

think what happens a lot time is I think people have expectations that because a veterinarian or a physician is prescribing or recommending something there is a certain degree of safety that goes along with that. I think that is true, but I think it needs to be communicated so that actually the client is making the decision for their pet in terms of whether or not they feel the risk is worth is. I don't think you can make guarantees, so I think yes. Since I gave a yes to the first question, I am having a hard time coming up with any recommendations. At least from the perspective of an epidemiologist that is gong to add additional information in terms of answering the question.

DR. CRAIGMILL: Thank you. Dr. Riddell.

DR. RIDDELL: I guess at the risk of sounding like an ogre, when you deal with a set of reactions that might by the World Health Organization be classified as rare or very rare, to get any kind of statistical power you are going to have to have large populations exposed to that, and so that suggests that I might be advocating using a population --- experiment. That is not the case. However, we have a product that may be potentially valuable and the compliance they shoot for, a very real disease in the canine population. We also need to know if it is safe, and several other good questions about its efficacy and the impact of

the microspheres on the immune system. They are all really important, but I think at some point in time to get the numbers that we are going to need to be able to truly evaluate this, it is going to have to go back into general maybe educated use, and it might be that we might have to be required sponsor-initiated educational program for those users that would not be unlike what a current sponsor has to do for the human potential ill effects from ---. While that is a bias that is taking a group that biased towards using it, making them responsible, and I think they are responsible for making sure that appropriate data for cases of adverse events reported and followed up on I think is probably only one of the true ways we have going to have to evaluate this. I don't think that the data sets like Banfield other than Banfield are going to be out there.

DR. CRAIGMILL: Thank you. Dr. Trepanier.

DR. TREPANIER: I also believe that a prospective study is ideal, although because I think the pet owning population is very sensitized to this drug, you may not be able to find a lot of people willing to allow their dogs to receive it. Also it would be very expensive. So I was trying to think of ways to work with the data that is available to try to get more information about perhaps mechanisms and is there a safe way to label this drug and

make it -- a safer way to label this drug. Certainly I think doing a meta analysis is one thing to consider. There are certainly other large computerized veterinary networks like VCA. The Animal Medical Center is also a very large practice. There might be ways to mine that data in a manner that is similar to Banfield that you have other data sets that could confirm or conflict with what was reported from Banfield. Also if you are trying to get at mechanisms, certainly the anaphylactic reactions may be very different from the convulsions. They probably are. But if there are serum --- from these patients that have had convulsions, do they have very high moxidectin concentrations? Or if there are CSF or brains from these patients. So are some of these patients having abnormally high release from this drug. I know that C-max concentrations were very narrow in initial studies, but that was with a very small group of dogs. We are talking about outliers here. We are expecting to have outlier responses.

Then the other issue of microfilaria being present and possibly triggering anaphylaxis, is there a way to go back and look at heartworm endemic versus heartworm non-endemic areas and see if instances of anaphylaxis is different in those two groups. Because that may be away, a less expensive way to try to get at that information.

DR. CRAIGMILL: Thank you. For my own comments, basically everything has been covered pretty much by all the other panel members. I think that if possible a retrospective case control while it might not add a whole lot to the data might be reassuring. That a prospective study with a very large clinical trial would be probably the only way to put this issue to bed, and that such a study would need to be -- the protocol would need to be agreed upon in advance by FDA and also Fort Dodge. In other words, work together to figure out what you need to answer this question if you are going to do that. In that, that would require the use of the drug in a large number of animals, and to do that I think a very good public education and informed consent program for the owners would be necessary. Because even at low rates, one out of 10,000, if that one is yours it is still a rate of one, and people need to know that is a risk. If you are completely risk adverse you need to warn people away from using this compound, or probably just about anything in that regard.

The other last -- first of all I should say that I am academician, which means I don't have to have practical ideas.

(Laughter.)

DR. CRAIGMILL: It would seem to me that this

issue is looking on the horizon for all heartworm products now that the awareness has been raised, and that this might be something that a consortium of the manufacturers of these drugs ought to get together and work on them together, even though they are competing on the sales. Why don't you get the data together to show that these products really are safe, or let's say acceptably risky to use.

I don't have any other comments at this point. Aleta, is there anything else we need to do? So we will turn it over to Dr. Sundlof for the benediction.

DR. SUNDLOF: Thank you, Mr. Chairman. I just want to thank you and the committee and all the folks who have participated in this today. As you see, these are very weighty decisions that we have before us. In my imagination I was hoping we would get a clear signal.

(Laughter.)

DR. SUNDLOF: But realistically I was prepared that we would not get that, and that appears to be where we are. So we will take the comments back to CVM. We will certainly have a thorough discussion based on what we heard today from this group, and we will come to some conclusion. Hopefully we can take into account especially the answers to the second question that I think laid out some very attractive possibilities for further investigation

in this. So again thank you all. I know it was a lot of information that you had to go through in a very short period of time, and with the weather and everything it was wonderful that you could all make it. A few people didn't. So thanks again, and I wish you a safe trip home.

(Whereupon, the meeting was adjourned at 5:14 p.m.)

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